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CONTENTS

Certification of Clinical Pathologists. FREDERICK H. LAMB 261
Erythroblastosis in the Newborn and in Early Childhood. ASHER YAGUDA.... 266
The Oral Glucose Tolerance Test. GORDON B. MYERS AND RICHARD M. McKEAN 299
A Simple Method of Supplying Carbon Dioxide in Jars for Bacteriologic Cultures. LUTHER THOMPSON 313
Reform in County Government and the Coroner's Office. OSCAR T. SCHULTZ... 316
Standardizing Sickle Cell Method and Evidence of Sickle Cell Trait. JAMES S. P. BECK AND CHARLES S. HERTZ 325
Malignant Hemangioma. B. MARKOWITZ 333
Editorial 339
Book Reviews 342
News and Notices 346

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American Journal of Clinical Pathology

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CERTIFICATION OF CLINICAL PATHOLOGISTS*

FREDERICK H. LAMB

220 Main Street, Davenport, Iowa

Soon after the turn of the century, medical education in this country approached a dangerous crisis in its history. There had been a rapid increase in the number of medical schools, far outstripping the need therefor. Plants with inadequate physical equipment and doubtful teaching facilities were vying with each other in a manner but little short of hectic to increase the enrollment of students. Had this trend continued unbridled, the plight of medical education, and consequently the practice of medicine itself, would have deteriorated to a point which challenges the imagination.

But, toward the end of the first decade, an important, restraining influence began to make itself felt, which effectively stemmed the rising tide of new schools. The Council on Medical Education and Hospitals of the American Medical Association was organized and soon thereafter, inaugurated standards of education. These the medical schools were required to meet in order to secure the council's approval. So influential was the firm leadership in this movement that a number of the less substantial institutions faded from the picture. "Fewer and better medical schools" was the watchword of the council, and its ability to make schools conform to its high standards has been the crowning achievement in the control of medical education.

The segregation of medical practice into special branches has proceeded apace without heretofore much really effective supervision. But just as the time came in the history of undergraduate education when the influence of a strong guiding hand was

* Presidential Address read before the Fourteenth Annual Convention of the American Society of Clinical Pathologists, Atlantic City, New Jersey, June 7 to 9, 1935.

needed, so has that period arrived in the development of graduate education and special practice. Many warranted criticisms have been leveled at abuses and deficiencies in special medical practice. Most of these are traceable directly to the inadequate preparation of those so engaged, and this can be corrected. The best answer and most practicable remedy so far devised seems to be the institution of a system of self regulation, initiated by the more responsible element in the various specialties. Failure in this direction will certainly result in the invocation by society of general protective measures of a far-reaching nature. Even now in specific instances redress is claimed and cases find their way into courts, an eventuality which tends to bring discredit on the whole medical profession.

A limited number of special examining boards has been organized and is functioning; notably, the American Boards of Ophthamology, of Otolaryngology, of Obstetrics and Gynecology, and of Dermatology and Syphilology. More recently the Boards of Psychiatry and Neurology and of Radiology have been duly organized. In addition to the five branches of medicine just referred to, seven others are recognized at present as suitable fields for the certification of specialists.

Sensing the need in this movement for a governing or coordinating body in graduate medicine, the Council on Medical Education authorized in 1933 the organization of an Advisory Board for Medical Specialties. It is fortunate, indeed, for those specialties, which now have the project of certification under advisement, that this forward step has been taken. The Advisory Board has already given consideration to many of the problems common to all specialties. It has formulated standards of administration, designed to reduce duplication of effort to a minimum. Moreover, it is provided that when organizations have been regularly approved by the Advisory Board, they may thereafter be represented on that board, thus retaining an interest in its control. Since this is a distinctly educational movement in the field of graduate training, it is not contemplated that there will be any dues chargeable to member organizations. Of course, traveling and other expenses of representatives in attend-

ance at annual meetings must be provided for in some manner by the organization. Thus much of the pioneer work in this important movement has been done.

At the last annual meeting of the American Society of Clinical Pathologists, your president was authorized by resolution to appoint a committee to consider the matter of examination and certification in clinical pathology. A report on the deliberations of this committee (composed of Drs. A. H. Sanford, J. H. Black, and A. H. Braden) will be submitted to the membership at the annual meeting.

Since ways and means have already been provided for the establishment of extra-mural relations, that is, with the Advisory Board, with related national organizations and with other examining boards, it remains for us, as a body to decide whether or not we wish to espouse the movement. The character of our daily work and the nature of our associations seems to indicate that examination for and certification of fitness to engage in the practice of clinical pathology would be very appropriate and desirable. Consummation of the project should have a wholesome and regulating influence. Ultimately, it should be the means of correcting a number of long standing irregularities, not only on the part of individuals, but on the part of those institutions which are not averse to rendering a form of lip service.

On several occasions it has come to the attention of the Board of Censors of this Society that in certain hospitals the management has been concerned merely with hiring some one to act as clinical pathologist in order that the institution might thus secure or retain a favorable rating. Competent pathologists have been replaced by mediocre hirelings in the name of economy when it was found such tactics would be tolerated. On the other hand, there are examples of deficiency on the part of individuals engaged in the practice of clinical pathology, which should unquestionably be rectified. The examination of laboratory technicians conducted by the Registry of Technicians has revealed a surprising lack of fundamental education among them. To some extent, this is a reflection on their training. This lack of a

proper sense of responsibility on the part of hospitals, and incompetence on the part of laboratory personnel, where it exists, is the crux of the situation to be rectified.

It is too much to expect that certification alone will eliminate all evils. Yet, it should become eventually a potent factor in segregating good intentions from bad, and serve as an inspiring objective. It does not require prophetic vision to see that as more and more of those engaged in the practice of other specialties make the sacrifice incident to their own examination and certification, they will insist on some sort of regulation in the practice of clinical pathology, with which they are bound to be more or less concerned.

As representative of the group most actively engaged in the clinical, surgical, and anatomical application of pathology, it is logical that we assume the initiative in this project. Naturally those engaged in teaching and research are subject to the regulations of their own institutions. Likewise in those instances where one's entire time is devoted to a single subdivision of pathology, certification in the usual meaning of the term may be less significant. On the other hand the coöperation of teaching and research workers in this general movement would be most desirable.

Under the general plan of the Advisory Board, we should seek the coöperation of the American Society of Pathologists and Bacteriologists, also that of the Section of Pathology and Physiology of the American Medical Association, since they are the two most closely allied organizations. Thus, the examining board in pathology would consist of two or three representatives from each of these organizations, as well as from our own. Candidature for examination would be open to any legally licensed physician, whose qualifications in preliminary training and experience would meet the requirement specified by the board. Such nomination of the board's personnel would insure so far as possible that independence of action and impartiality in the conduct of its affairs which is essential.

If, after consideration of the report of the committee on certification, a tentative plan shall receive the endorsement of the

society, I hope it will finally merit and receive a full measure of support from the entire membership especially during the formative period. Our representatives on the examining board should be chosen with great care. In their association with other nominees, they should strive to reflect the sentiment and purpose of this society so far as possible. To be sure, many of the details for the successful operation of the plan will have to be worked out by the board itself, such for example, as its incorporation and the adoption of a constitution. There should prevail a spirit of tact, fair play, and a willingness to compromise differences on the part of all concerned. In these respects, and finally, in that of resolute leadership I have faith that the American Society of Clinical Pathologists will not be found wanting.

ERYTHROBLASTOSIS IN THE NEWBORN AND IN EARLY CHILDHOOD*

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It is the intention of this paper to present a group of cases which, while apparently showing different clinical pictures, are similar in their hematologic and histologic manifestations, and because of this similarity are being classed under the name "erythroblastosis," and to add to this group a fourth condition which has recently been separated from the group of splenic anemias (von Jaksch's disease) and shows essential features which to my mind identify it with the erythroblastoses. As the basis for this terminology depends upon hematologic evidence of increased production of immature erythrocytes, and upon the histologic demonstration of persistent and exaggerated extramedullary and perhaps medullary hematopoiesis, the material used in this paper was selected because of the presence of these features in the clinical and necropsy data in cases from the maternity and pediatric services of the Newark Beth Israel Hospital.

All of the diseases gathered under this title have been recognized clinically as distinct entities for many years. It was not until lately that the similarity in their pathologic pictures has been noted. Shridde,[55] in 1910, reported that he consistently found evidence of marked extramedullary hematopoiesis in three cases of congenital hydrops fetalis. Rautmann,[49] in 1912, while studying blood formation in fetal edema, applied the term "erythroblastosis" to this condition. Von Gierke,[63] in 1921, noted the similarity of the histologic findings in icterus gravis to those described by Shridde[55] in congenital hydrops. Frank,[25]

* Read before the Thirteenth Annual Convention of the American Society of Clinical Pathologists, Cleveland, Ohio, June 8 to 11, 1934.

in 1926, described the presence of excessive extramedullary hematopoiesis in the necropsy material from a case of anemia of the newborn.

A condition in infancy and early childhood whose identity has formerly been lost in the miscellaneous group of childhood anemias classified as Von Jaksch's disease, has recently been shown by Cooley and Lee[12] to be of the nature of an excessive erythroblastic production.

The conditions mentioned above will be considered separately and cases of each type presented, together with necropsy data, which I believe will demonstrate clearly the similarities of their pathologic pictures.

ERYTHROBLASTOSIS. TYPE: CONGENITAL HYDROPS

Congenital hydrops of the fetus has been recognized for many years, instances appearing in the literature during the early seventeenth century. Ballantyne[3] described congenital hydrops as a

> morbid condition of the fetus characterized by general anasarca, the presence of fluid effusions in the peritoneal, pleural and pericardial sacs and usually by edema of the placenta; and resulting in the death of the fetus or infant before, during or very soon after birth.

While congenital hydrops of the fetus is reported as being of rare occurrence, it is probably more common than formerly believed, many cases not being recognized or reported. Clifford and Hertig[11] estimate its occurrence as one in 2000 to 3000 births. The disease occurs most frequently in premature fetuses, who usually are stillborn, although many of them are born alive and die within a few hours of birth. The longest recorded duration of life in this condition was six days.

There appears to be no preference for either sex. It apparently is not racial in its distribution, but there is a definite familial tendency. Most of the cases reported appear to be in multiparous mothers, although instances have been cited in primiparas. Hydramnion is frequently present, together with edema of the placenta. Occasional cases have been reported in which there

was slight or moderate jaundice or anemia associated with the edema.

Ballantyne felt that general dropsy of the fetus was not a pathological entity, but rather "a group of structural alterations due to several different causes." Many mechanical conditions which could be established as the etiologic factor in the production of congenital hydrops fetalis have been listed by Capon[8] and others.

There were, however, cases reported in the literature both by Ballantyne and many others since, in which no macroscopic evidence of vascular or lymphatic obstruction, or other mechanical causes of hydrops could be found. Among the earliest attempts in the right direction to explain these so-called idiopathic cases of congenital hydrops was the report by Sanger[53] in 1888, who believed that he was dealing with a fetal type of myeloid leukemia. The credit for first calling attention to the fact that this type of fetal edema presented a characteristic histologic picture must go to Shridde,[55] who, in addition to the typical generalized edema, noted a striking enlargement of the spleen and some enlargement of the liver in his series of three cases. These two organs microscopically showed marked evidence of extramedullary hematopoiesis, with a marked predominance in erythropoiesis which was also present in the lymph nodes and to a lesser degree, but not constantly, in several of the other organs. The bone marrow in all cases was hyperplastic. In addition to the hematopoiesis, Shridde[55] observed, especially in the liver, a marked deposit of hemosiderin. Practically all of the liver cells showed a marked iron reaction. He also found in the blood of his cases large numbers of nucleated red cells.

Rautmann, confirmed these observations and because he considered the process a pathologic proliferation of the erythroblastic tissues, initiated the term "erythroblastosis" for this condition.

CASES

(1) A male, born dead July 7th, 1932. His mother, an apparently normal white woman 35 years of age, had been married for 11 years and had been pregnant four times. The first and second children were normal and are still living and well. The third child, born in 1926, was stillborn at 6 months, cause

unknown. The fourth pregnancy terminated in a miscarriage at three months in 1927, cause undetermined. During this pregnancy the mother had no illnesses nor did she suffer from any edema. At the Obstetrical Clinic on June 29th, 1932, it was estimated that she should deliver about September 1st, 1932 and because she appeared to be rather large a note was made to re-examine her in one month for twins. Her blood pressure was normal, Wassermann and Kahn tests negative; the urine essentially negative.

On July 7th at 8 a.m. the patient was admitted to the hospital because of profuse vaginal bleeding. Examination revealed a marginal placenta previa and the vagina was packed with iodoform gauze. Four hours later the patient was delivered spontaneously of a stillborn male child. The child was pale at birth, 45.75 cm. long, weighed 2.5 kg. The estimated age of the child was seven months and it was noted that the child had a markedly distended abdomen and marked edema of the scrotum.

Necropsy showed a moderate pitting edema of the skin, both scrotal sacs filled with fluid and a large amount of clear yellow fluid in the peritoneal cavity and both pleural cavities. The heart showed no anatomic defects and the lungs were atelectatic but otherwise negative. The spleen was markedly enlarged, had a deep brownish red color and was soft and cellular in consistency. The liver was markedly enlarged, showed a smooth and glistening brownish red surface and on section was granular in appearance. The other organs showed no evidence of any gross abnormalities. There was a moderate edema of the meninges.

Anatonic diagnosis: Congenital universal hydrops. Splenomegaly. Enlargement of the liver. Ascites. Pleural effusion. Edema of the brain.

Microscopic examination

Liver: There was a tremendous cellularity of the liver which with the high power objective was seen to be due to a marked hematopoietic activity in the liver. The liver cells were compressed and atrophic. The liver capillaries were dilated and filled with erythrocytes many of which were nucleated. The hematopoietic activity, for the most part, was outside of these capillaries and consisted of groups of large basophilic cells having large, pale nuclei with two or three nucleoli. Surrounding these larger cells could be seen many nucleated erythrocytes in various stages of maturation. Cells, apparently of the myeloid series, could also be made out. Many eosinophiles, both myelocytes and mature, could be seen. The section of the liver studied showed such diffuse hematopoiesis that it was difficult to localize it to any one portion of the liver lobule; however, there was a tendency for the foci to be more numerous around the portal system. Sections stained for hemosiderin showed iron pigment in fairly large amounts situated for the most part in the liver cells.

Spleen: The spleen showed an absence of normal histology. The splenic follicles were small and almost entirely absent. The pulp was dense and showed a characteristic dilatation of the sinusoids, many of which were empty and others

contained blood and myeloid cells. There was some increase in fibrous tissue, but for the most part the pulp was infiltrated by hematopoietic cells similar to

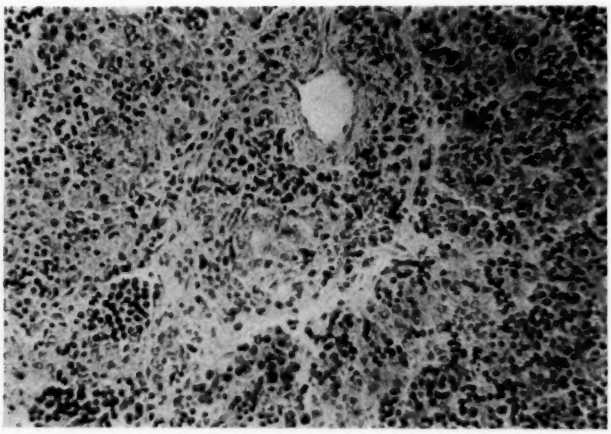

FIG. 1. (A) Microscopic findings (low power) in the liver in erythroblastosis from a case of congenital hydrops, showing diffuse foci of hematopoiesis with compression and atrophy of the liver cells (280 ×).

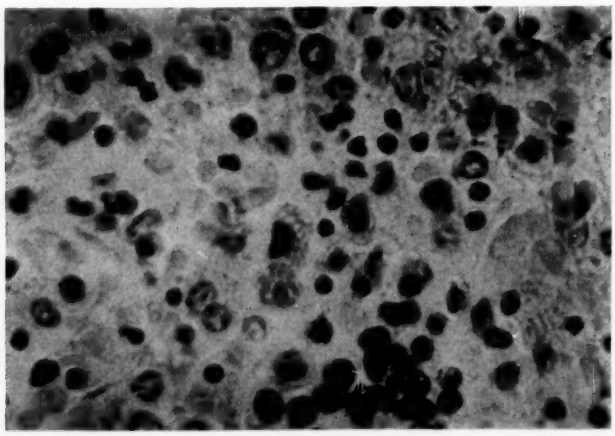

FIG. 1. (B) High dry power (1130 ×) of a hematopoietic focus showing both erythropoiesis and myelopoiesis.

those in the liver, with marked erythropoietic activity predominating. Iron stains showed practically no iron pigment; an occasional phagocytic cell con-

taining a small amount of pigment could be seen. The lining cells of the sinusoids and the connective tissue around the blood vessels and septa showed no pigment.

Small foci of erythropoiesis were also found in the pancreas and in the kidney in relationship to the smaller blood vessels and were not extensive. Unfortunately, the bone marrow was not studied in this patient.

The other organs showed no evidence of extramedullary blood formation or other significant lesions.

Microscopic diagnosis: Erythroblastosis.

Two additional cases of congenital hydrops occurred in post mortem material available to me and which gave in the main similar findings to those reported above.

(2) Born September 29th, 1931 of Italian parents. The mother was 46 years of age and this was her seventh pregnancy. Two previous pregnancies had terminated in stillbirths, cause undetermined. She came to the hospital in what was estimated to be her eighth month because of hemorrhage and was immediately delivered of an enormous male child weighing 5.9 kg. and showing marked maceration. There was also present a polyhydramnion and an edema of the placenta. The entire body was edematous. The abdomen was protuberant and on incision showed a marked ascites. The pleural cavities also contained some clear yellow fluid. Aside from enlargement of the liver and spleen and rather advanced autolysis of all the organs, no other gross abnormalities could be found. Microscopic examination showed definite areas of hematopoietic activity in the liver and spleen, in spite of the marked autolysis of all the organs.

(3) Born spontaneously on November 11th, 1930 of a healthy white mother who had had one other child. Past history of the mother was entirely negative. The child was a large female infant weighing about 3.4 kg. and upon birth it was noted that the abdomen was protuberant and filled with a large firm tumor which extended from the right flank to the left nipple line and downward to the level of the umbilicus. The child expired about four hours after birth and autopsy showed a large amount of pale straw colored fluid in the peritoneal cavity with a markedly enlarged spleen and liver. The other organs were grossly negative. Microscopic examination showed the characteristic findings of erythroblastosis.

Etiology and pathogenesis

The etiology of erythroblastosis with congenital hydrops is obscure. Several theories as to the etiology and pathogenesis have been advanced and these chiefly resolve themselves into two groups. The first a group which believes as Shridde[55] does

that the erythroblastosis is a reparative process and is secondary to some etiologic factor which serves to destroy the blood of the fetus during intra-uterine life and that it is this anemia of the fetal blood which stimulates increased blood formation. Hemolytic anemia,[45] various toxic factors, lues,[6] nephritis in the mother and metabolic disturbances of pregnancy[58] have all been considered as possible causative factors in the production of this condition.

Rautmann disagreed with Shridde[55] that the marked hematopoiesis indicated a reparative process. He believed that he was dealing with a primary erythroblastosis, not a reparatory, but a pathologic proliferation of the erythroblastic tissues.

Various explanations of the edema have been stated in the literature. Toxic factors,[10] anemia,[8,65] disturbance of the circulation due to compression by the hematopoietic foci,[37] pathologic metabolism of the fetus,[56] disturbance of placental function[58] and nephrosis in the fetus[67] have all been offered as etiologic factors causing the edema.

ERYTHROBLASTOSIS. TYPE: ICTERUS GRAVIS

Icterus gravis has been differentiated from ordinary icterus neonatorum and recognized in the literature as a clinical symptom complex frequently since the beginning of this century. Buchan and Comrie,[6] in 1909, called attention to the marked anemia, the numerous immature and nucleated erythrocytes and the necropsy findings of extramedullary hematopoiesis of the erythroblastic type. They however, placed no primary significance upon these features, considering them an indication of a rapid reparatory blood formation resulting from a hemolytic type of anemia. Rehn,[50] and Yllpo,[69] reported cases of icterus gravis with nucleated erythrocytes in the circulation and necropsy finding of active hematopoiesis in the liver, but they also considered these findings as a secondary phenomenon. It was not until 1921 that the true import of this picture was pointed out. At that time, Von Gierke, studying the necropsy material of a child dead of icterus gravis with kernicterus, called attention to the fact that the pathology of his case fitted in with the description of erythro-

blastosis as given by Shridde, and suggested the probable relationship between icterus gravis and congenital hydrops.

Clinically, cases of icterus gravis are readily differentiated from icterus neonatorum by the fact that in the former, the icterus is present at birth or develops shortly after birth, and progresses rapidly, while in icterus neonatorum, the development of the jaundice does not occur until the third or fourth day and is of relatively mild degree. Frequently, attention is called to the intra-uterine development of the jaundice by the finding of a yellow vernix caseosa.

There appears to be no racial incidence but there is a marked familial tendency. Rolleston[52] has pointed out that the cases usually occur in families where there are a large number of pregnancies. The first and second-born frequently escape, and then there is a definite occurrence of icterus in successive pregnancies. Smyth[59] reported seven successive siblings with icterus gravis.

Physical examination reveals, in addition to the jaundice, a more or less severe degree of anemia with slight to moderate enlargement of the liver, and usually a marked enlargement of the spleen. Petecchial and ecchymotic hemorrhages are frequently noted in the skin and mucous membranes.

The blood count reveals a hyperchromic type of anemia with the number of cells reduced out of proportion to the hemoglobin content, giving a color index well above 1.0. There are many nucleated erythrocytes in the smears. Buhrman and Sandford[7] have reported as high as 213,000 nucleated erythrocytes per cubic millimeter of blood, although usually the number is much less, between 50,000 to 100,000 per cu. mm. The erythrocytes also show variations in size and shape and many basophilic nonnucleated red cells are found. The leukocyte count shows a mild to a moderate leukocytosis, with a shift to the left and occasionally myelocytes and myeloblasts appearing in the peripheral blood. The platelets are normal or slightly reduced in number. Coagulation time is normal and bleeding time has been reported prolonged, this probably being due to the severe jaundice.

As the disease progresses, jaundice becomes increasingly in-

tense, the child shows a marked apathy, becomes drowsy and usually dies following severe convulsions. Death occurs in about eighty per cent of the children[52,28] within the first week of life. In the other cases, the children do not seem to become toxic and in spite of the severe jaundice, do well and after a period of several weeks to several months, the jaundice disappears and the blood returns to normal after a longer period of secondary hypochromic anemia.

In those cases where necrospy has been performed, it was found that the entire skin surface and mucous membranes and all of the organs were deeply bile-stained. The liver was slightly enlarged; the spleen was usually markedly enlarged; a slight amount of bile-stained fluid was usually present in the serous cavities; the bone marrow showed a deep red color throughout. The brain may show some edema of the pia-arachnoid and occasionally, on cross-section, the basal ganglia have a characteristic yellowish mottling which has been referred to in the literature as "kernicterus." Microscopic examination shows marked evidence of hematopoieses in the liver and in the spleen, with occasionally some liver cell damage as indicated by areas of necrosis. In the hematopoietic foci of the liver and spleen, erythroblastic predominance is apparent. The bone marrow may show considerable activity with the myeloid cells especially involved. Bile thrombi in the bile canaliculi of the liver were reported in about fifty per cent of the cases. Much bile pigment was seen in the liver cells; there was a considerable amount of iron pigment in the spleen and in the Kupffer cells of the liver.

CASE REPORT

(4) Admitted to the hospital May 8th, 1933 at 4 a.m. The child was a three day old female baby markedly jaundiced "with a somewhat typical cerebral moan," moving its arms about in a slow fashion. There was no rigidity or flaccidity of the extremities. The temperature was 99.8°. No history was obtainable except that the child had been jaundiced since birth. Death occurred three hours after admission. The clinical diagnosis was "probable brain injury."

The necropsy showed a normally developed female infant with a marked icterus of the skin and mucous membranes. There was a small amount of clear yellow fluid in the peritoneal cavity. All of the internal organs were markedly

icteric but otherwise negative grossly except the spleen and liver which were enlarged, the spleen more so than the liver. There were no abnormalities of the gall bladder or biliary duct system. The spleen on section showed a dark granular surface with little evidence of lymphoid follicles. The liver on section was greenish yellow in color and showed areas of pinpoint to pinhead size which were a dark brownish red in color and of different consistency and appearance than the surrounding liver tissue. The brain showed no evidence of any pathology except for an icteric staining of the basal ganglia. The bone marrow everywhere appeared hyperplastic. Blood smears taken post mortem showed numerous normoblasts in the peripheral blood.

Microscopic examination showed the typical histologic features described under congenital hydrops. In addition to the marked erythroblastic activity the liver cells contained much dark brown granular pigment which did not give the characteristic staining reaction for iron. The Kupffer cells contained some iron pigment. The spleen was relatively free of iron pigment.

Etiology and pathogenesis

In discussing the etiology and pathogenesis of icterus gravis we must consider separately the jaundice, the anemia and the erythroblastic process before taking up their relationship to each other.

During the last days of intra-uterine life and the first few hours of extra-uterine life there exists in the infant a polycythemia.[40] In the days immediately following birth there is a rapid drop in the number of erythrocytes and hemoglobin.[68] This occurrence is a post-natal adjustment from an environment requiring the presence of polycythemia for the maintenance of oxygenation, to one in which no such extraordinary measures are necessary. This rapid drop in the blood count and hemoglobin is accomplished through an increased fragility of the erythrocytes of the peripheral blood[27] and causes an increased bilirubin content of the blood serum which may or may not be present in sufficient amount to give a yellow tint to the skin. This physiologic icterus neonatorum is prevented from becoming excessive by some anti-hemolytic substance elaborated by the infant.[28]

While Yllpo[69] sees no reason for differentiating familial icterus gravis from ordinary icterus neonatorum, believing both of these conditions to be simply a continuance of fetal liver function, the histologic data points to liver damage as the cause of the intense

jaundice in icterus gravis, whereas in icterus neonatorum the jaundice is presumably due to a faster production of bilirubin than the liver cells are able to excrete. Klemperer,[34] in a study of necropsy material from three cases of icterus gravis found extensive liver damage which he compared to acute yellow atrophy. While severe jaundice such as this has been shown to occur in newborn sepsis[35, 19] and in syphilis,[42] these conditions have not been factors in true icterus gravis of the familial type.

In icterus gravis as in congenital hydrops the anemia has been explained as being the result of marked blood destruction due to excessive hemolysis, the nature of the hemolytic agent being unknown. Colemic intoxication,[50] defective production of antihemolytic substance[28] and marked fragility of the immature erythrocytes[1] found in such large numbers in this condition have all been blamed for the severe anemia which these cases show. Here again, as in congenital hydrops, there are two views as to the nature of the erythroblastosis, opinion being divided between the reparatory and primary nature of this process.

ERYTHROBLASTOSIS. TYPE: ANEMIA OF THE NEWBORN

In recent years a small group of cases have been recorded in literature in which an otherwise apparently normal infant was born showing a marked pallor, or developed a marked pallor within a few days or weeks after birth. These children were born of normal parents with no clinical or laboratory evidence of lues or other transmissible disease. There was a familial tendency towards newborn disease in many of the cases reported. There did not appear to be any racial incidence. The children were most often full-term. In about 50 per cent of the cases reported, jaundice usually mild, was present. Physical examination failed to reveal any gross abnormality except for the extreme pallor, but in about 60 per cent of the cases, a palpable spleen, which was not remarkably enlarged. The blood picture showed a moderate to severe hyperchromic anemia with moderate anisocytosis, poikilocytosis and basophilia. In most cases, a few normoblasts were present although they did not form as striking a part of the picture as in the previous conditions. The leukocytes ranged

from leukopenia in some of the cases to marked leukocytosis in others. The majority of the cases reported in the literature showed a mild leukocytosis of from 10,000 to 20,000 leukocyte cells per cubic millimeter. Occasional myelocytes and myeloblasts have been frequently reported, but these did not appear in large numbers. The blood platelets were usually normal to increased in number. Coagulation and bleeding time were normal. Resistance to hypotonic salt solution was usually normal but has been reported as decreased.

The course of the disease was usually benign, the child, in spite of its pallor, developed normally, retained its food and with transfusion to overcome the anemia, made a complete recovery in from a few months to a year. Deaths, however, have been reported.

Finkelstein,[24] in a general lecture on anemia in children, mentioned the occurrence of congenital anemia but cited no instances. While credit for the first description of a case of anemia of the newborn is generally given to Ecklin,[20] 1919, there appears in the literature a report of what is probably an earlier case. Buchan and Comrie, reported "four cases of congenital anemia with jaundice and enlargement of the spleen." Three of their cases are undoubted instances of familial icterus gravis with anemia, but the second child in family "A" presented a hematological and clinical picture compatible with the diagnosis of anemia of the newborn as described by later authors and similar to one of the cases to be presented. Since Ecklin's report several cases of anemia of the newborn have been reported and have been enumerated by Diamond et al.[18]

Frank, pointed out the similarity of the histologic findings of this disease to those of erythroblastosis of congenital hydrops, and suggested that anemia of the newborn was also an erythroblastosis. This observation has since been confirmed by others. The necropsy findings showed no abnormalities of the organs, except that the liver and spleen were enlarged and there was a marked general anemia. Small hemorrhages were reported by Schleussing[54] in his case. The microscopic examination showed marked extramedullary hematopoiesis in the liver, spleen and

bone marrow. Schleussing described many immature erythrocytes and leukocytes in these hematopoietic foci. He also found mitotic nucleated erythrocytes in the bone marrow.

CASES

(5) A white female child 9 days old admitted to the hospital with a history of anemia since birth. She had been a normal full term child but had not ap-

TABLE 1

CASE 6. (BIRTH: MAY 2, 1931)

HEMATOLOGICAL CHART

NEWBORN ANEMIA

DATE	ERYTHROCYTES	HEMOGLOBIN*	LEUCOCYTES	DIFFERENTIAL CELL COUNT								PLATELETS
				Polymorphonuclears	"Stab"-forms	Metamyelocytes	Myelocytes	Eosinophiles	Lymphocytes	Monocytes	Nucleated erythrocytes per 100 leucocytes	
1931	*millions*	*per cent*										
May 4	1.69	39	17,500	49	12			4	30	5	15	
" 7	2.19	53	13,850	46	4			3	41	6	5	
" 9	1.35	35	18,000	55	2			7	40	1	5	
" 13	2.77	57	10,400	29	8		4	6	48	5	3	240,000
" 16	3.03	58	8,000	40	6			4	45	5	3	
" 18	2.56	40	8,950	50	3			4	34	9	3	
" 25	3.02	62	10,300	24	2			2	70	2	1	
June 1	2.86	54	9,000	38	1			1	58	2	3	
" 15	2.90	55	8,050	29	4	2		6	58	1	3	
1932												
July 10	4.20	72	9,200	42	4	0	0	3	48	3	0	

* Sahli.

peared as red as a newborn baby should. The child nursed well until two days before admission, at which time she vomited after feeding. Since birth the child had become slightly yellow and the hands paler. There were no hemorrhages. The family history was entirely irrelevant. Upon admission to the hospital examination showed a well formed, well nourished baby looking very pale and ill. Physical examination was negative except for distended abdomen in which the spleen was palpable three fingers below the costal margin and the liver was also enlarged and palpable three fingers below the costal margin. The

blood count showed 95,640 nucleated cells, of which 38,000 were leukocytes and the rest nucleated erythrocytes. The hemoglobin was less than 10 per cent and the erythrocytes less than 800,000. The differential cell count showed polymorphonuclear neutrophiles, 35 per cent; large lymphocytes, 12 per cent; small lymphocytes, 32 per cent; myelocytes and meta-myelocytes, 21 per cent. A clinical diagnosis of myelogenous leukemia was made. The patient died on the evening of admission.

Necropsy showed an extremely pale female infant with a grossly enlarged liver and spleen. Aside from severe anemia the other organs were of normal appearance. Section of the liver and spleen showed what appeared to be an infiltration of these organs with a greyish red substance. The bone marrow was intensely red.

A necropsy of this patient was performed in 1925 and unfortunately the tissues in this case were lost, so that no microscopic examination could be made. However, in the light of present day knowledge of anemia of the newborn, and with the clinical and hematological evidences as presented in the protocol, I believe one is justified in classing this case as one of anemia in the newborn.

(6) Male child born May 2nd, 1931 of a normal white mother 32 years of age. At birth, which occurred at 10 a.m., it was noted that the child appeared pale and at 4:30 p.m. of the same day jaundice was noticed. By 7 p.m. or 9 hours after delivery the jaundice was marked and the child had projectile vomiting which continued the next day. On May 4th the child was apathetic, did not cry and had twitchings of the arms and legs. Stools were green in color and contained yellow curds. The blood count showed a severe anemia with many nucleated erythrocytes in the differential smear. Repeated blood counts showed persistence of a severe anemia with erythroblasts in the peripheral circulation which improved somewhat with transfusions. A clinical diagnosis of anemia of the newborn was made. The jaundice entirely disappeared by the time the child left the hospital. The child started gaining weight and at the time of discharge from the hospital on the 20th day, weighed the same as on the day it had been born. After leaving the hospital blood counts over a period of one month showed persistence of the anemia which was slightly less severe. Nucleated erythrocytes in small numbers were present at every examination. One year later the blood count showed an entirely normal picture.

Etiology and pathogenesis

The etiology of anemia of the newborn, similar to the conditions previously reported, is very obscure. Susstrunk[62] interpreted the case presented by him clinically as an aplastic type of anemia, and attempted to explain the contradictory histologic findings of active extramedullary and medullary hematopoiesis on the possibility that the picture of aplastic anemia in the newborn

does not agree anatomically with that of the adult. Happ[29] explained this condition on the basis of a congenital deficiency of the erythrocyte forming elements in the bone marrow. He came to this conclusion because he found deficient erythropoiesis in the bone marrow, with marked erythropoietic activity in the liver and spleen. Lichtenstein[39] believes that the mechanisms of these anemias include absolute or relative functional insufficiency of the hematopoietic organs and that a lack of material for blood building, a depot defect in the supply of iron. Schleussing thinks that the hematopoietic system in these cases has lagged behind the other organs in its development and, depending upon how premature this system is, the inhibited development can be overcome and the patients recover.

Stransky[61] divided anemia of the newborn into two groups, basing his distinction upon the presence or absence of immature blood cells in the circulating blood. He found that in fatal cases, the greatest numbers of nucleated erythrocytes occurred and were due to faulty or incomplete development of the organs of hematopoiesis, while in cases of lesser severity, which recovered, only a few embryonal forms occurred and there was temporarily insufficient hematopoiesis.

ERYTHROBLASTOSIS OF INFANCY AND EARLY CHILDHOOD. TYPE: ERYTHROBLASTIC ANEMIA

Cooley and Lee, presented five cases of splenomegaly in children with anemia and peculiar bone changes which showed the clinical syndrome which has commonly been classified as von Jaksch's anemia. Cooley, Witwer and Lee,[14] supplementing their previous report, felt that their cases had enough common distinctive features to be grouped separately and apart from the nondescript group of splenic anemias known as von Jaksch's disease, and later Cooley[15] suggested the term "erythroblastic anemia" for this type of case.

Erythroblastic anemia was defined by Baty, Blackfan and Diamond[5] as a

> disturbance of the hematopoietic system characterized by a constant, racial and familial incidence, a typical appearance, a progressing anemia with large

number of nucleated erythrocytes in the peripheral blood, enlargement of the spleen, destructive changes in the bone, and finally, histologic lesions in the bone marrow and spleen.

A familial tendency in erythroblastic anemia is evident from even a cursory survey of the cases reported. Two, three and even five siblings affected with this condition have been reported as occurring in the same family. The racial incidence among Mediterranean peoples is so strong that at the present time no single proved case has been reported outside this group.

The onset of the disease usually suggests a congenital origin. The first symptom, usually pallor, has been reported as being present since birth[66] or soon after birth.[4] Several cases have been first seen as late as nine years after birth.[36] Following the appearance of the pallor, the disease progresses gradually and soon the second prominent feature of the clinical picture, enlargement of the abdomen, is noted. Frequently, there is a history of some intercurrent infection immediately preceding the pallor and abdominal enlargement.

Physical examination shows an enlarged head due to enlargement of the cranial bones, a sunken bridge of the nose, rather prominent eyes and a muddy, yellow pallor of the skin, creating the impression of a child of Chinese parentage, a characteristic which caused Cooley[14] to label this as "Mongoloid appearance." Another characteristic feature is the enlargement of the abdomen, especially on the left side, due to an enlarged spleen. Frequently, these children are small in stature, a factor which further emphasizes the enlarged head. Examination of the internal organs usually reveals, in addition to the enlarged spleen already mentioned, some enlargement of the liver and an enlargement of the heart, which is probably secondary to the long standing anemia.

Rather characteristic changes occur in the bones which may be detected roentgenographically and have been described by several authors.[51, 32, 23] These roentgen changes are progressive in nature. During the early stages of the disease, or in mild cases, there is first noticed an increased porosity of the medullary portion of the bones, giving a mottled appearance. Later on, as the disease

progresses, the changes assume two very characteristic pictures, the one occurring in the skull, and the other in the long bones. The skull shows a thickening of the diploe, which may be increased to several times its normal thickness. The outer and inner tables of bone are very thin. Between these two tables can be seen peculiar, perpendicular hair-like striations. These have been reported so numerous and fine that they have been referred to by Baty as "hair standing on end." The long bones also show rather characteristic changes including a widening due to an increase in the medullary portion of the bone, and rarefaction of the medulla. There is also noted an atrophy of the compact bone of the cortex and a peculiar trabeculation of the medulla, which is especially noticeable in the small bones, but can be made out in all of the bones, especially at the metaphyseal end.

Another major characteristic of erythroblastic anemia is the hematologic picture. The general picture is that of a moderately severe hypochromic anemia with a persistent leukocytosis, and a large number of immature and nucleated red blood cells in the smears. Kato and Downey,[33] studying the blood smears of the original cases presented by Cooley, together with some presented by Diamond, Blackfan and Baty and others, described very clearly and in detail, the picture as seen in the blood smear. The most essential feature is the presence of numbers of nucleated erythrocytes in all stages of maturation. There are times when the number of these may be comparatively small, while at other times, they may reach enormous figures. Some of the cases studied show normoblasts in their primitive stages (erythroblasts). One of the most characteristic and unusual groups of cells are the immature erythroblasts which have a markedly basophilic cytoplasm and contain no hemoglobin. All stages and gradations from this to the hemoglobin containing normoblasts are seen. Mitotic and amitotic division are found in some of the smears. Many erythrocytes without nuclei, but with intensely basophilic cytoplasm are found. Cooley and Lee[16] called attention to a cell which they considered almost pathognomonic of this condition. These cells show an irregular distribution of hemoglobin, with clumping, giving a mottled appearance. Another

striking characteristic is the marked variation in the amount of hemoglobin contained by the individual erythrocytes, some being hyperchromic and others decidedly hypochromic.

The leukocytes show the picture of mild hematopoietic stimulation. There is a constant leukocytosis with a shift to the left, and occasional myeloblasts and myelocytes in the blood smear.

The blood platelets are usually normal in number but may be slightly increased. Bleeding and coagulation time are normal. Reticulocytes are usually present in increased numbers. Although some authors report 10 per cent, or more, in my case the highest reticulocyte count was 3.7 per cent. The fragility of the erythrocytes has usually been reported as normal. An occasional report of increased resistance to hypotonic salt solution can be found in the literature. The icteric index is frequently slightly increased. Following transfusion or intercurrent infection, in some cases a high icteric index has been noted. The van den Bergh is usually reported as a positive indirect reaction.

Following splenectomy, a peculiar and characteristic increase in the erythroblastemia occurs and tends to differentiate this group of cases from other types of splenic anemia.[30] This exaggeration of the erythroblastemia is persistent and constant.

Pathology

Necropsy descriptions of changes in the bones were given by Schultz,[57] Baty et al. and Whipple and Bradford.[64] They are in practical agreement as to the anatomic and histologic findings, even though they disagree as to the mechanism by which these changes are brought about. The long bones show hyperplasia of the marrow, with a widening of the marrow cavity, which is filled with dense red marrow. There is a thinning of the cortex of these bones, with the formation of trabeculae of connective tissue and osteoid which penetrate the medulla of the bone. The skull is thicker than normal and at the same time, softer. This is due to a hyperplasia of the diploe of the cranial bones. The cross-section shows a pinkish, spongy surface with an atrophic thin layer of compact bone forming both the inner and outer tables. The bone marrow studied in five cases coming to autopsy

showed in all an extreme hyperplasia. In three of these cases[66, 5, 64] there was a predominance of erythroblastic elements. Schultz found few cells which could be identified as erythrocyte precursors, the entire process appearing to be leukoblastic. This type of reaction was also described by Koch and Shapiro. The bone marrow from the necropsy presented in this paper showed a definite preponderance of erythroblastic activity.

The liver may or may not show evidence of extramedullary hematopoiesis, and when present, is usually slight. However, degenerative changes, chiefly fatty, are described in the central zones of the liver with large amounts of fine, granular pigment in the cells about the portal system, which give a positive iron stain.

The changes (see table 2) which take place in the spleen have been described by various pathologists. Stillman,[60] in studying three spleens removed at operation, felt that the splenic changes were progressive and consisted of increasing fibrosis and myelodization of the pulp with concomitant decrease in the size of the splenic follicles, due to the increasing pulp rather than to the fibrosis. The histologic descriptions of the spleen agreed in most respects, but disagreed on one rather essential and perhaps most important point.

In all of the spleens examined there was present a certain degree of fibrosis, atrophy and decrease in the number of splenic follicles and increased pulp through which course wide sinuses. A scant amount of iron-containing pigment was usually found. On the question of extramedullary hematopoiesis however, there is no such unanimity of opinion. Where hematopoiesis is reported as present, the erythroblastic predominance of this process is noted. In all cases reported, eosinophilic cells were present in varying numbers, usually many. A peculiar type of cell reaction is reported by Whipple and Bradford, and mentioned by Fries et al.[26] This cell is foamy in appearance, has phagocytic tendencies, and resembles the type cell seen in Gaucher's disease. The significance of this finding is not at all clear.

The changes in the other organs are those secondary to severe, prolonged anemia and are not relevant to this discussion.

TABLE 2

HISTOLOGY OF HEMATOPOIETIC SYSTEM AT NECROPSY. ERYTHROBLASTOSIS. TYPE: ERYTHROBLASTIC ANEMIA

		O. T. SCHULTZ QUOTED BY COOLEY WITWER AND LEE	WOLLSTEIN AND KRIEDEL	BATY, BLACKFAN AND DIAMOND	WHIPPLE AND BRADFORD	KOCH AND SHAPIRO	YAGUDA
SPLEEN	FIBROSIS	Present	Present	Present	Present	Present	Present
	SPLENIC CORPUSCLES	Atrophic	Scant	Few inactive	Small	None	Atrophic
	PULP	Dense		Abundant	Dense	Fibrotic	Dense
	SINUSES	Wide	Wide	Prominent	Prominent	Wide	Wide
	HEMOSIDERIN		Scant in sinuses —living cells	Small amount	Almost absent	In phagocytes	Scant
	HEMATOPOIESIS	Absent	Present	Extensive	None	Present	Present
	Myeloid	Absent	Present	Present		Present	Present
	Eosinophils	Present	Present	Present	Present		Present
	Erythroblastic	Absent	Marked	Chiefly	None	Not mentioned	Marked
LIVER	HEMATOPOIESIS	None	Myeloid	May or not	None		Slight
BONE MARROW	TYPE OF REACTION	Myeloid	Normoblastic	Erythroblastic	Erythroblastic	Leukoblastic	Erythroblastic

Prognosis and course

One of the distinctive features of this group of cases, separating it from the type of case von Jaksch had in mind, is the progressive course of the disease, with fatal termination. The course seems to be more acute in those children in whom the disease is recognized early. There appears to be no tendency to remission, although some temporary improvement follows repeated blood transfusions. Infection, which occurs in these children with average frequency, tends to aggravate the disease and produce a more profound anemia.

Cooley[16] believes that splenectomy may retard the progress of the disease, and Capper[9] pleaded for splenectomy as a method of prolonging the life of the patient. Hitzrot[30] reported one case alive fourteen years after splenectomy for von Jaksch's disease, in which, following splenectomy, there was a characteristic and persistent erythroblastemia which was present fourteen years after operation. In spite of this, Baty, Blackfan and Diamond do not feel that splenectomy in any way alters the symptomatology or clinical course of the disease, and Wollstein and Kreidel[66] agree that splenectomy for erythroblastic anemia is a failure.

Death ensues usually within a few years due to secondary changes provoked by the prolonged severe anemia, or to intercurrent infection.

CASES

(7) Admitted to the hospital on July 20, 1929 at the age of seven months with a diagnosis of splenic enlargement and anemia. The child was born of Italian parents at full term and was entirely normal until at the age of four months the family first noted an anemia. Following this the anemia became progressively more marked and the spleen and liver became enlarged. The family history shows that the mother had had seven children of which two were alive and well and five had died during infancy. There is a definite history of two siblings having died from a similar condition, one at seven months and one at 17 months.

Physical examination at the time of admission to the hospital showed a poorly developed white baby with a muddy pallor which developed into a subicteric tint of the skin. The mucous membranes were blanched and there were several large palpable lymph nodes in the neck. The abdomen was distended due to a marked enlargement of the spleen and a slight enlargement of

the liver. Temperature on admission was normal, the pulse rapid (144) and respirations 26. Mantoux test and serologic examination of the blood for lues were negative. The blood count showed a hemoglobin of 30 per cent (Sahli), 1,700,000 erythrocytes, total nucleated cells 198,000, of which only 30,000 were leukocytes and the rest nucleated erythrocytes. The differential cell count showed 58 per cent polymorphonuclear neutrophiles, 40 per cent lymphocytes and 2 per cent monocytes. The bleeding time was 3½ minutes, coagulation time 6½ minutes, fragility test showed normal resistance to hypotonic solution. The urine was negative and showed no bile and no increase in urobilinogen. X-ray pictures of the lower extremities showed the typical changes of erythroblastic anemia as described above. The child failed to respond to several transfusions and died on August 27, 1929. The clinical diagnosis was von Jaksch's anemia.

Necropsy revealed an emaciated white female child with a protuberant abdomen and an extreme pallor of the skin and mucous membranes. The liver was enlarged, weighed 385 grams and on section was pale and showed fatty changes in the center of the lobules. The spleen was enlarged, firm and weighed 110 grams. There was no peri-splenitis. On section the cut surface was a rather pale red color. The Malpighian corpuscles were visible and there appeared to be small areas of deeper red granular tissue scattered throughout the pulp. Aside from changes due to the severe anemia and some petecchial hemorrhages the other organs were entirely negative. There were however a number of retroperitoneal and peri-aortic lymph nodes which were enlarged and of a deep red color. The bone marrow everywhere was deep red in color and extremely hyperplastic. Anatomic diagnosis: von Jaksch's anemia; splenomegaly; generalized lymph node enlargement; hyperplastic bone marrow; marked anemia of all the organs.

Microscopic examination

Liver: The liver showed marked fatty degeneration of liver cells. In the liver capillaries which were dilated could be seen nucleated erythrocytes of all types. Many immature cells of both the myeloblastic and erythroblastic type were seen, occasionally in foci which might be considered as hematopoietic. There was a moderate amount of iron pigment present in the liver cells.

Spleen: The spleen showed an increase in fibrous tissue. The follicles were scant and atrophic. The pulp was fairly dense and composed of dilated sinuses which were empty except for occasional nucleated cells and a cellular tissue which upon higher magnification was seen to be composed of hematopoietic tissue with erythroblastic activity predominant. Many myeloid cells were present, especially of the eosinophilic variety. The predominant factor however, was that of erythropoiesis. Iron was scant and for the most part was found in the cells lining the sinusoids and in free phagocytes; however, occasional areas of more marked iron deposit could be seen around a few of the blood vessels and scattered in an occasional lymph follicle.

Lymph nodes: Mesenteric lymph nodes showed a picture similar to that in

the spleen with evidence of hematopoiesis going on actively in the bone marrow. The bone marrow showed a marked hyperplasia and was extremely cellular. A large part of the cellularity was due to myeloid hyperplasia, but many foci

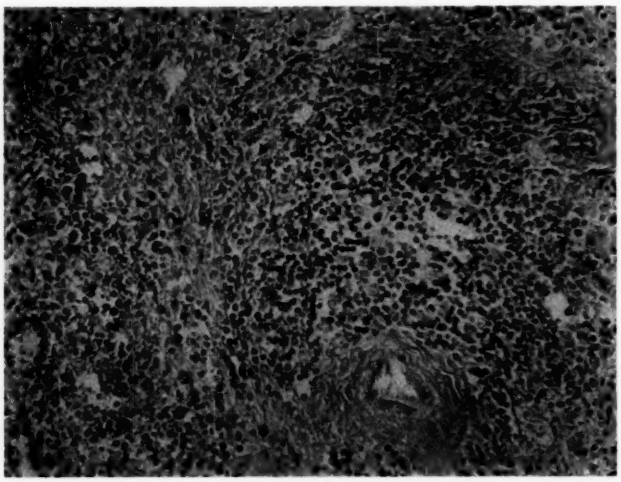

FIG. 2. (A) Microscopic findings in the spleen in erythroblastosis from a case of erythroblastic anemia showing atrophic Malpighian follicle, dense pulp with dilated sinusoids and hematopoiesis in pulp (280 ×).

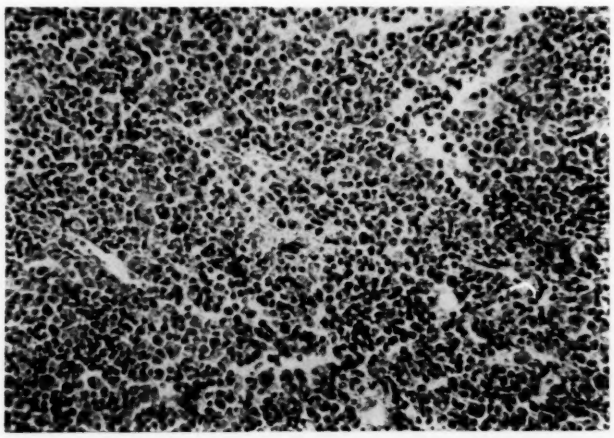

FIG. 2. (B) Microscopic appearance of bone marrow in a case of erythroblastic anemia showing marked erythropoiesis (280 ×).

were present which showed extremely active erythropoiesis. Near the center of these erythropoietic areas were large immature cells having a basophilic cytoplasm and surrounding these were nucleated erythrocytes in various stages of maturation. Megakaryocytes were present in normal numbers.

Other organs: Aside from dgenerative changes, no evidence of other pathology was found. There was no extramedullary hematopoiesis in the other organs.

Final diagnosis: Erythroblastic anemia.

(8) Born of Greek parents on March 31, 1932, full term, normal female child. The mother was 31 years of age and had had one previous child who was at this time one year old and while slightly pale was apparently normal. After leaving the hospital the child apparently was well until four months of age, although there had been a slight increasing pallor during these four months. During her fifth month the pallor increased and the child gained no weight. At the ninth month vomiting occurred together with marked loss of weight. At this time the child was admitted to the hospital because of these complaints.

Physical examination on admission showed an extremely pale white female infant about 10 months of age with a large head, prominent forehead and a tendency towards mongoloid facies. The heart was enlarged to percussion and hemic murmurs were heard. The abdomen was protuberant and there was a markedly enlarge spleen and slightly enlarged liver. A few palpable lymph nodes were present in the axillae and groins. The blood picture showed the characteristic findings of erythroblastic anemia. (See table 3.) X-ray examination of the skull and long bones showed the characteristic findings seen in erythroblastic anemia.

The child has since the first admission been repeatedly transfused and the blood picture can be followed in table 3. There have been several intercurrent infections and a temperature resembling the Pel-Ebstein type was noted. Repeated X-ray examinations have shown an exaggeration of the previously reported findings in the bones of the skull and extemities. When last seen on April 24, 1934, the child still showed progression of the disease.

A blood count done on the sister of this child at the age of two years showed a moderate anemia with many immature red blood cells of the anisocytotic and basophilic type and a few nucleated red blood cells.

Here, as in the other types of erythroblastosis, the etiology is obscure and the discussion of pathogenesis gives rise to many theories. These consider in the main the same mechanism by which this condition might be brought about, as were discussed in the other types of erythroblastosis.

Cooley, at first found many similarities between erythroblastic anemia and a group of hemolytic anemias (congenital hemolytic jaundice, sickle cell anemia), and suggested that the clinical

picture was due to hemolysis in each instance of the abnormal erythrocytes under the influence of the spleen. Later, because of lack of substantiating evidence of marked hemolysis, and because

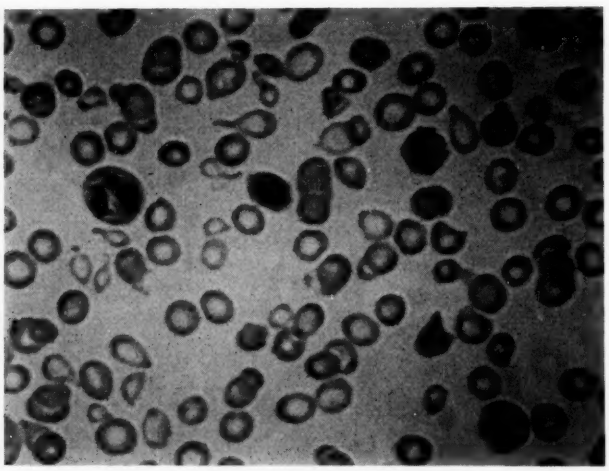

FIG. 3. (A) High dry power of blood smear from case of icterus gravis showing characteristic erythroblastemia (1130 ×).

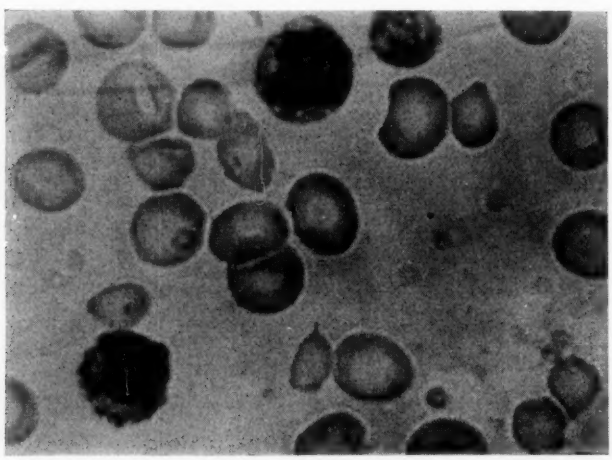

FIG. 3. (B) Oil immersion of blood smear from a case of erythroblastic anemia showing immature basophilic non-nucleated red cell and normoblast (2400 ×).

TABLE 3

CASE 8. ERYTHROBLASTIC ANEMIA

DATE	ERYTHROCYTES*	HEMOGLOBIN	LEUKOCYTES	DIFFERENTIAL CELL COUNT									NUCLEATED ERYTHROCYTES			RETICULOCYTES	PLATELETS	BLEEDING TIME	COAGULATION TIME	CALCIUM	PHOSPHORUS	ICTERIC INDEX	VAN DEN BERGH	FRAGILITY TEST	WASSERMANN AND KAHN
				Polymorphonuclears	"Stab"-forms	Metamyelocytes (young forms)	Myelocytes	Myeloblasts	Eosinophiles	Basophiles	Lymphocytes	Monocytes	Microblasts	Monoblasts	Erythroblasts										
1933	*millions*																								
2–16	2,66	31	30,600	35	12	4	3	3	1	1	37	4	23	60	2	2.0	172,000	5		10.2	2.5	15		0.42–0.3	
2–20	3,72	49	25,100	33	4	3	1	2	3	0	46	8	4	60	3										
2–23	4,41	60	26,000	29	3	1	1	1	2	1	51	11	4	46	0	2.2	200,000	3		10.0	2.94	31		0.42–0.26	Neg.
3–29	2,41	36	21,150	9	4	0	0	1	3	0	80	3	9	34	2	2.0	230,000								
5–4	2,67	35	18,650	28	6	1	1	1	5	1	53	3	0	33	0										
5–12	4,18	75	12,000	33	7	2	0	0	3	0	50	5	0	12	2										
7–21	2,36	38	22,600	28	11	4	2	1	2	2	47	2	8	33	1										
8–28	2,20	36	22,900	36	2	0	1	0	2	1	53	4	14	44	3										
9–21	2,49	37	11,500	35	15	1	1	0	1	1	40	6	0	3	0										
9–29	4,00	71	10,900	37	9	1	1	0	0	3	33	16	1	1	0										
12–15	2,84	37	19,500	29	4	0	0	0	1	0	65	1	0	26	0										
1934																									
1–18	2,60	30	19,850	36	7	0	0	0	3	1	46	7	0	36	1										
3–10	2,04	30	28,000	44	16	3	1	1	1	1	25	6	2	14	1	2.0	320,000								
4–24	1,93	26	26,400	31	9	2	1	1	2	1	49	4	3	48	3	3.7	185,000	4	7			13.3	0.44	0.40–0.28	Neg.

* Sahli.

of the similarity of the bone marrow findings to those in pernicious anemia, Cooley and Lee denied the essential hemolytic nature of this type of anemia and believed it to be due to an inadequate supply of proper material for blood building. Whipple and Bradford agreed with this concept and suggested some disturbance in pigment metabolism as the deficiency factor. Baty et al. preferred to think of an inherited developmental defect in the hematopoietic system as the cause of the anemia. The erythroblastemia is considered by Evans and Happ[22] as an infantile type of response to factors which would, in the adult, cause ordinary secondary anemia.

The bone changes are dependent upon hyperplasia of the marrow with expansion of the marrow cavity and pressure on the soft infantile bone. Cooley, Witwer and Lee believe that the replacement of the cellular marrow by trabeculae of connective tissue and osteoid indicate beginning exhaustion of the hydroplastic process. Wollstein and Kreidel point to the experiments of Johnstone[31] as proving this concept to be true. Whipple and Bradford, on the other hand, do not believe that simple hyperplasia is sufficient to cause these changes. They prefer to consider the change as due to a disturbed metabolism, either racial or associated with ductless gland inbalance, or some other unknown factor.

DISCUSSION

The evidence presented strongly points to a marked similarity, if not etiologic identity of the conditions under discussion. Shridde mentioned the similarity of the histologic picture of congenital hydrops to that of pseudoleukemic anemia of Luzet,[41] which was probably a case of erythroblastic anemia. von Gierke brought familial icterus gravis into the group of erythroblastoses, and Frank pointed out the essential erythroblastic nature of anemia of the newborn. That these three conditions are various manifestations of the same process is subscribed to by Diamond et al., Abt,[1] and Parsons et al., who reviewed in detail their various points of similarity and interminglings. Parsons and Hawksley[44] described a case of anemia in a newborn infant which, had it been

seen later in infancy, would have been classified as von Jaksch's anemia. Akerran[2] presented a case of anemia following icterus gravis which showed a "remarkable congruence" with the form of infantile anemia known as von Jaksch's anemia. Pinkerton[47] described a case of "erythroblastosis" in a seven and one-half year old child.

All of these conditions are essentially congenital, thus congenital hydrops is always present at birth. Icterus gravis has been described as commencing during intra-uterine life, anemia of the newborn is present at or immediately after birth, and the first symptom of erythroblastic anemia has been described as being present at birth by Wollstein and Kreidel, and soon after birth by Baty et al. Cooley believes that this condition is congenital in nature.

The tendency to occur in more than one member of the same family has been described in all of these conditions by many observers. Erythroblastosis has also appeared in different members of the same family in several clinical forms, such as congenital hydrops and icterus gravis reported by Plaut[48] and also by Diamond et al. DeLange[17] described the finding of twins with erythroblastosis, one showing the picture of congenital hydrops and the other of icterus gravis. Buchan and Comrie's cases contained one case with a typical picture of newborn anemia in a family where three other children died of icterus gravis, and in Ecklin's case of anemia of the newborn, a previous sibling had died of icterus gravis.

There is apparently no racial factor in erythroblastosis associated with hydrops, jaundice or anemia, but in erythroblastic anemia a definite racial tendency is apparent, and all cases reported so far have been in offspring of Mediterranean peoples. However, too few cases of this type of anemia have appeared in the literature to definitely close this question.

A point which has apparently escaped attention and which I believe may be of etiologic significance is the striking fact that practically all of the cases of erythroblastosis, regardless of type, have occurred in the children of women, who at the time of birth, were well advanced in their child-bearing period, practically all

of them being over thirty years of age and many of them past thirty-five. Many authors have called attention to the fact that these conditions usually spare first and second children, and that many of the cases have occurred in multiparous women in their later pregnancies.

In all the sub-divisions of this classification the cases were first recognized as related conditions because of the finding of marked hematopoiesis in extramedullary loci, a return to a fetal type of hematopoiesis. The identity of the changes of the spleen, the liver and bone marrow of these various clinical groups is the strongest argument for including them under one classification. Etiologically they seem to be thrown together. While many of the opinions place these conditions in the group of hemolytic anemias, the data available is against this hypothesis. The normal fragility of the erythrocytes, the absence of marked increase of urobilinogen in the urine and the absence of marked hemosiderosis in the organs of blood destruction all point against excessive hemolysis as an etiologic factor in this disease.

Inhibition of development of the hematopoietic organs with persistence of fetal type of blood formation has been advanced to explain the hematologic and pathologic findings, by Eichelbaum[21] in congenital hydrops; Abt in icterus gravis; Schleussing in anemia of the newborn, and Baty et al. in erythroblastic anemia of infancy and childhood. While none of these authors can explain the cause of this lack of development, Kratziesen and Ballhorn[38] think that it may be due to a primary metabolic disturbance of the function of the fetal liver.

After carefully reviewing the various opinions offered in the literature as to the nature and cause of erythroblastosis, and weighing the evidence it seems to me that the view expressed by Cooley and Lee[16] in 1930 that the process is due to an inadequate supply of proper material for blood building is the most logical explanation of this process. Whether it is due to defective transfer or absorption of these materials from the mother to the child, or to some fundamental lack or change in pigment metabolism, or some internal secretion deficiency as suggested by Whipple and Bradford cannot be stated.

The similarity of the bone marrow picture in erythroblastic

anemia to the findings of Peabody[46] in pernicious anemia during the period of relapse, has been quoted by Baty et al. Stillman found a great similarity in the blood picture of erythroblastic anemia to that shown by pernicious anemia during an erythroblastic crisis, and Naegeli[43] felt that these two conditions were closely related pathologically. The fact that all types of erythroblastosis occur most frequently in offspring of women past thirty years of age, suggests the possibility that this deficiency might perhaps be due to the exhaustion of some maternal hormone necessary for stimulation of proper blood formation in the fetus.

All of the above factors, in my opinion, point to the fetal type of erythropoiesis found in erythroblastosis as a pathologic hypertrophy and hyperplasia of the blood forming organs during fetal life analogous to the hypertrophy and hyperplasia of the thyroid during iodine insufficiency.

REFERENCES

(1) Abt, A. F.: Erythroblastosis in icterus gravis neonatorum. Jour. Ped., **3:** 7–30. 1933.

(2) Akerran, Y.: A contribution to the knowledge of "primary" anemic states in early infancy. Acta. Paed., **14:** 142–159. 1932–33.

(3) Ballantyne, J. W.: Manual of antenatal pathology and hygiene. The foetus. Edinburgh: Wm. Green and Sons, 288–297. 1902.

(4) Baty, J. M.: Anemia in infants and children. New Eng. Jour. Med., **203:** 319–324. 1930.

(5) Baty, J. M., Blackfan, K. D., and Diamond, L. K.: Blood studies in infants and in children. Am. Jour. Dis. Child., **43:** 667–704. 1932.

(6) Buchan, A. H. and Comrie, J. D.: Four cases of congenital anemia with jaundice and enlargement of the spleen. Jour. Path. and Bact., **13:** 398–413. 1909.

(7) Buhrman, W. L. and Sanford, H. N.: Is familial jaundice of new-born infants erythroblastosis? Am. Jour. Dis. Child., **41:** 225–235. 1931.

(8) Capon, N. B.: General oedema of the foetus. Jour. Obst. and Gyn., **29:** 239–273. 1922.

(9) Capper, A.: The nature of von Jaksch's anemia and the effect of splenectomy. Am. Jour. Med. Sc., **181:** 620–629. 1931.

(10) Chiari, H.: Ein Beitrag zur Kenntnis der sogenannten foetalen Erythroblastose (i.e. einer Form der angeborenen allgemeinen Wassersucht). Jahrb. f. Kinderh. u. Phys. Erz., **80:** 561–568. 1914.

(11) Clifford, S. H. and Hertig, A. T.: Erythroblastosis of the newborn. New Eng. Jour. Med., **207:** 105–113. 1932.

(12) Cooley, T. B. and Lee, P.: A series of cases of splenomegaly in children with anemia and peculiar bone changes. Trans., Am. Ped. Soc., **37:** 29–30. 1925.

(13) Cooley, T. B.: von Jaksch's anemia. Am. Jour. Dis. Child., **33:** 786–797. 1927.

(14) Cooley, T. B., Witwer, E. R., and Lee, P.: Anemia in children (with splenomegaly and peculiar changes in the bones)—report of cases. Am. Jour. Dis. Child., **34:** 347–363. 1927.

(15) Cooley, T. B.: Likenesses and contrasts in the hemolytic anemias of childhood. Am. Jour. Dis. Child., **36:** 1257–1262. 1928.

(16) Cooley, T. B., and Lee, P.: Erythroblastic anemia. Am. Jour. Dis. Child., **43:** 705–708. 1932.

(17) deLange, C.: Icterus familiaris gravior und Hydrops foetalis cum erythroleukoblastosi. Acta. Paed., **13:** 292–299. 1932.

(18) Diamond, L. K., Blackfan, K. D., and Baty, J. M.: Erythroblastosis fetalis and its association with universal edema of the fetus; icterus gravis neonatorum, and anemia of the newborn. Jour. Ped., **1:** 269–309. 1932.

(19) Dunham, E. C.: Septicemia in the new-born. Am. Jour. Dis. Child., **45:** 229–253. 1933.

(20) Ecklin, T.: Ein Fall von Anämie bei einem Neugeborenen. Monatschr. f. Kinderh., **15:** 425–436. 1919.

(21) Eichelbaum, H. R.: Über die Erythroblastose (Hydrops-congenitus) der Neugeborenen und ihre Beziehung zum Icterus neonatorum. Arch. f. Gynae., **119:** 149–162. 1923.

(22) Evans, F. A., and Happ, W. M.: Secondary anemias of infants. A study of so-called infantile splenic anemia or anemia infantum pseudoleukemica. Bull. Johns Hopkins Hosp., **33:** 1–12. 1922.

(23) Feingold, B. F., and Case, J. T.: Roentgenologic skull changes in the anemias of childhood. Am. Jour. Roent., **29:** 194–202. 1933.

(24) Finkelstein, H.: Ueber die Anämien des frühesten Kindesalters. Berl. Klin. Wochenschr., **48:** 1829–1833. 1911.

(25) Frank, E. S.: Aangeboren anaemie door erythroblastose. Nederl. Tijdschr. u. Geneesk., **70:** 1384–1389. 1926.

(26) Fries, J. H., Duhan, E., and Shair, H. M.: Erythroblastic anemia. Jour. Ped., **2:** 487–492. 1933.

(27) Goldbloom, A., and Gottlieb, R.: Icterus neonatorum. Am. Jour. Dis. Child., **38:** 57–74. 1929.

(28) Hampson, A. C.: Grave familial jaundice of the newly-born. Lancet, **1:** 429–432. 1929.

(29) Happ, W. M.: Discussion in proceedings of the American Academy of Pediatrics. Jour. Ped., **1:** 637. 1932.

(30) HITZROT, J. M.: Unclassified type of splenomegaly in children. Ann. Surg., **88:** 361–379. 1928.

(31) JOHNSTONE, E M.: Changes in the morphology and function of the bone marrow after splenectomy. Arch. Surg., **5:** 159–187. 1922.

(32) KARSHNER, R. G.: Roentgen studies of the bones in certain diseases of the blood and hematopoietic system. Am. Jour. Roent. and Rad. Ther., **20:** 433–439. 1928.

(33) KATO, KATSIYI, AND DOWNEY, HAL: The hematology of erythroblastic anemia. Folia hemat., **50:** 55–67, 1933.

(34) KLEMPERER, P.: Icterus gravis of the newborn. Am. Jour. Dis. Child., **28:** 212–226. 1924.

(35) KNOEPFELMACHER, W.: VI. Der "habituelle Icterus gravis" und verwandte Krankheiten beim Neugeborenen. Ergebn. d. inn. med. u. Kinderh., **5:** 205–221. 1910.

(36) KOCH, L. A., AND SHAPIRO, B.: Erythroblastic anemia. Am. Jour. Dis. Child., **44:** 318–335. 1932.

(37) KOVÁCS, F.: Über die angeborene allgemeine Wassersucht der Frucht an der Hand eines Falles. Zentralb. f. Gynak., **54:** 1948–1954. 1930.

(38) KRATZEISEN, E., AND BALLHORN, W.: Über angeborene Erythroblastose der Leber. Ztschr. f. Kinderh., **39:** 314–334. 1925.

(39) LICHTENSTEIN, A.: Hematological studies of premature babies during infancy with particular reference to anemic conditions. Abstracted by B. S. Denzer. Arch. Ped., **43:** 738–762. 1926.

(40) LIPPMAN, H. S.: A morphologic and quantitative study of the blood corpuscles in the newborn period. Am. Jour. Dis. Child., **27:** 473–526. 1924.

(41) LUZET, C.: Étude sur les anémies de la première enfance et sur l'anémie infantile pseudo-laucémique. These de Paris, 1891.

(42) MACCALLUM, W. B.: Textbook of pathology. 4th edition. Philadelphia: W. B. Saunders Co., 739. 1929.

(43) NAEGELI: Quoted by STILLMAN.

(44) PARSONS, L. G., AND HAWKSLEY, J. C.: Part V. The haemolytic erythronoclastic anemias of later infancy and childhood. Arch. Dis. Child., **8:** 184–210. 1933.

(45) PARSONS, L. G., HAWKSLEY, J. C., AND GITTINS, R.: Studies in the anaemias of infancy and early childhood. IV. The haemolytic (erythronoclastic) anemias of the neonatal period; with special reference to erythroblastosis of the new born. Arch. Dis. Child., **8:** 159–183. 1933.

(46) PEABODY, F. W.: The pathology of the bone marrow in pernicious anemia. Am. Jour. Path., **3:** 179–202. 1927.

(47) PINKERTON, H.: Aleukemic leukemia and atypical leukemoid conditions. Arch. Path., **7:** 567–600. 1929.

(48) PLAUT, A.: Erythroblastosis, kernikterus and congenital hydrops. Arch. Path., **4:** 137–139. 1927.

(49) RAUTMANN, H.: Über Blutbildung bei fötaler allgemeiner Wassersucht. Beitr. z. pathol. anat., allgem. pathol., **54:** 332–349. 1912.

(50) REHN, H.: Zur Kasuistik des habituellen familiären Ikterus der Neugeborenen. Jahrb. f. Kinderh., **75:** 358–361. 1912.

(51) REYNOLDS: Quoted by COOLEY, WITWER, AND LEE.

(52) ROLLESTON, H. D.: Grave familial jaundice of the newly-born. Practitioner, **104:** 1–7. 1920.

(53) SÄNGER, M.: Ueber Leukämie bei Schwangeren und ageborene Leukämie Arch. f. Gynak., **33:** 161–210. 1888.

(54) SCHLEUSSING, H.: Beitrag zu den sogenannten Anämien der Neugeborenen. Verhandl. d. deutsch. path. Gesellsch., **21:** 371–375. 1926.

(55) SCHRIDDE, H.: Angeborene allgemeine Wassersucht. Münch. med. Wchnschr., **57:** 397–398. 1910.

(56) SCHRIDDE, H.: Angeborene allgemeine Wassersucht. Deutsche med. Wchnschr., **37:** 432. 1911.

(57) SCHULTZ: Quoted by COOLEY, WITWER AND LEE.

(58) SCHUMANN, E. A.: A study of hydrops universalis fetus, with report of a case. Am. Jour. Obst., **72:** 961–980. 1915.

(59) SMYTH, J. S.: Notes on a further case of familial jaundice. Med. Jour. Australia., **2:** 268–270. 1931.

(60) STILLMAN, R. G.: A study of von Jaksch's anemia. Am. Jour. Med. Sc., **153:** 218–231. 1917.

(61) STRANSKY, E.: Beiträge zur klinischen Hämatologie im Säuglingsalter. X. Über die primäre Anämie der Neugeborenen. Zeitschr. f. Kinderh., **51:** 239–246. 1931.

(62) SÜSSTRUNK, G.: Schwerste Anämie bei einem Neugeborenen. Zeitschr. f. Kinderh., **38:** 587–592. 1924.

(63) VON GIERKÉ, E.: Kernikterus und Erythroblastose. Verhandl. d. deutsch. path. Gesellsch., **18:** 322–327. 1921.

(64) WHIPPLE, G. H., AND BRADFORD, W. L.: Racial or familial anemia of children associated with fundamental disturbances of bone and pigment metabolism (Cooley-von Jaksch). Am. Jour. Dis. Child., **44:** 336–365. 1932.

(65) WOOLLEY, P. G.: Fetal erythroblastosis: fetal erythroblastomatosis. Jour. Lab. and Clin. Med., **1:** 347–354. 1916.

(66) WOLLSTEIN, M., AND KREIDEL, K. V.: Familial hemolytic anemia of childhood—von Jaksoh. Am. Jour. Dis. Child., **39:** 115–130. 1930.

(67) YAGI, H., AND FUJIMARI, H.: Etiology of general congenital edema. Jap. Jour. Obst. and Gyn., **15:** 425–430. 1932.

(68) YAGUDA, A., AND GINZLER, A.: Hematology and hematopoiesis of the neonatal period. In Press.

(69) YLLPÖ, A.: Ueber des familiäre Vorkommen von Ikterus neonatorum gravis. Münch. med. Wochenschr., **65:** 98. 1918.

THE ORAL GLUCOSE TOLERANCE TEST

A Review of the Literature

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Bang[4] in 1913, introduced the first satisfactory and clinically applicable method for the quantitative estimation of the blood sugar. In the same year Jacobson[28] described a glucose tolerance test based upon the blood sugar curve after the ingestion of glucose. Since then such tests have been extensively used as diagnostic aids in diabetes mellitus, endocrinal disease, carcinoma, arthritis, et cetera. The literature has been reviewed in an attempt to evaluate the results and explain the shortcomings of the test.

Despite the vast amount of work done on the oral test, there is, as yet, no general agreement in technic nor in the interpretation of results. To evaluate the procedure, however, some standards are necessary, and the following have been most widely accepted. For the usual test carried out with single doses of 50 to 100 grams of glucose on patients fasting for 12 to 16 hours, the following three types of curve may be differentiated: (1) "normal" curve, which in venous blood shows a peak below 0.17 per cent and falls to the fasting level within two hours, and in capillary blood shows a peak below 0.20 per cent and falls below 0.12 per cent in two and one-half hours; (2) the "diabetic" curve, which attains a peak above 0.17 per cent in venous or 0.20 per cent in capillary blood, and is above 0.12 per cent at two hours and two and one-half hours respectively, and (3) the "borderline" curve which shows either a high peak or a delayed fall. With these criteria as guides in interpreting results, we shall attempt to support our contention that the oral glucose tolerance test is an unreliable diagnostic procedure in diabetes mellitus and is of questionable value in other conditions.

FAILURE OF AGREEMENT BETWEEN CLINICAL FINDINGS AND THE ORAL GLUCOSE TOLERANCE TEST

One reason for the apparent rarity of normal glucose tolerance curves in diabetes is that so many of the tests were carried out on patients with fasting blood sugars well above the accepted normal limit; that is over 0.12 per cent. (A glucose tolerance test is seldom needed to verify the diagnosis in such cases.) When the fasting level is below 0.12 per cent, the oral test is often inconclusive or misleading. To exemplify the foregoing statements, the curves in diabetes mellitus reported by twelve authors have been classified according to the standards described above, and are listed in table 1. Of the 200 curves tabulated, only fifty-seven began at a normal fasting level. Nineteen or one-third of the diabetics with normal fasting sugars failed to show "diabetic" curves. Nine of these curves were entirely normal* and ten "borderline."

It has long been known that a "diabetic" curve is occasionally found in perfectly normal individuals, and frequently in a number of diseases in which there is no clinical evidence of complicating diabetes at the time of the test, nor in careful subsequent examinations. Malmros[39] made tolerance tests on thirty-seven cases of "benign glycosuria" carefully observed over a long period of time, and found "borderline" curves in ten, "diabetic" curves in three. Many authors, in particular Gray[19] and Mosenthal[41]—have called attention to the frequency of "diabetic" curves in acromegaly, arthritis, cholecystitis, eczema, hypertension, hyperthyroidism, malignancy, melancholia, myxedema, Parkinson's syndrome, pernicious anemia, pneumonia, and many other conditions.

Since "normal" and "borderline" curves have been reported in undoubted cases of diabetes and, conversely, "diabetic" curves have been frequently found in non-diabetic individuals, one must conclude that a diagnosis of diabetes mellitus can neither be established nor excluded by the oral test alone.

* Since no attempt was made to exhaust the literature, the above statistics merely apply to well known individual work and not to the literature as a whole.

The oral test has been used extensively as a diagnostic aid in the endocrinopathies, and supposedly characteristic curves have been described for hyper- and hypothyroidism, hyper- and hypopituitarism, Addison's disease, et cetera, but numerous exceptions have been encountered. Glassberg[17] compared the oral glucose tolerance curves of twenty-two normal individuals with

TABLE 1

RESULTS OF VARIOUS AUTHORS USING ORAL GLUCOSE TOLERANCE TESTS IN DIABETES MELLITUS, CLASSIFIED ACCORDING TO THE CRITERIA GIVEN IN THE TEXT

AUTHORS	QUANTITY OF GLUCOSE ADMINISTERED	NUMBER OF CASES OF DIABETES MELLITUS	NUMBER OF CASES WITH FASTING BLOOD SUGAR LEVELS BELOW 0.12 PER CENT	CHARACTER OF CURVE IN PATIENTS WITH FASTING BLOOD SUGAR BELOW 0.12 PER CENT		
				"Diabetic"	"Normals"	"Borderline"
Williams and Humphreys	100 grams	16	5	2	1	2
Hamman and Hirschman	100 grams	9	6	6	0	0
Cummings and Piness	100 grams	14	8	2	2	4
Strouse	50–100 grams	3	3	1	1	1
Olmstead and Gay	1.75 grams/kg.	4	2	2	0	0
John	100 grams	93	14	14	0	0
Niemeyer	100 grams	8	8	3	4	1
Ralli and Shannon	100 grams	20	9	7	0	2
Glassberg	1.75 grams/kg.	6	1	1	0	0
Kern and Jones	1.75 grams/kg.	1	1	0	1	0
Hopkins	100 grams	9	0	0	0	0
Wishnofsky	100 grams	17	0	0	0	0
Total		200	57	38	9	10

those of twenty-six cases of hyperthyroidism, fifteen of hypothyroidism, eleven of hypopituitarism and ten of polyglandular disease. He found a very considerable overlapping of the curves of all five groups, and concluded that the oral test (using 1.75 gms. glucose per kg.) was of no value in differentiating these conditions.

Friedenwald and Grove[14] found "diabetic" curves in seventy-two out of seventy-five cases of carcinoma of the gastrointestinal

tract, and concluded that the test was of diagnostic value in this condition. Their results, however, were not confirmed by Biermer[7] who reported "normal" curves in almost 50 per cent of his cases. Further conflicting results have been obtained in many other conditions in which the test has been used.

LACK OF CONSISTENCY IN REPEATED CURVES

Serial glucose tolerance tests have been used to determine the severity of the diabetes,[47,57] to follow the course of arthritis, encephalitis,[33] and the response of myxedema and hyperthyroidism to treatment. Gardiner-Hill, Brett and Smith[15] performed glucose tolerance tests on several cases of myxedema before and after the administration of thyroid extract, and though their results were not uniform in all cases, the majority showed a "diabetic" curve before treatment and a tendency to return to normal under therapy. Denis, Aub and Minot[13] Janney and Isaacson[29] and Holcomb[22] in studying the effect of thyroidectomy on glucose tolerance in hyperthyroidism, generally found a high curve before operation and a normal one afterward. Pemberton and Foster[45] and Holsti[23] repeated the test at intervals during the course of arthritis, and finding, as a rule, a "diabetic" curve during the acute stages and a return towards normal during convalescence, concluded that there was a defect in carbohydrate metabolism, and recommended a low carbohydrate diet. Traut[53] and Archer,[2] on the other hand, were unable to correlate the shape of the curve with the stage of the arthritis. Furthermore, therapeutic results with the low carbohydrate diet have been, in the main, disappointing.

The tenability of conclusions based upon changing blood sugar curves in disease is dependent, of course, upon the close agreement of successive curves in the normal person. Lennox[37] made two or more oral tests under uniform experimental conditions on a large group of persons and reported his results in detail in thirty-one of these, including three healthy young adults, one case each of arthritis and hypertension and twenty-six cases of idiopathic epilepsy, all normal from the metabolic standpoint. Nine in-

dividuals, including the three healthy adults, showed "diabetic" curves in one test and "normal" in the other, four changed from "diabetic" to "borderline" curves, and two from "borderline" to "normal." Bock, Schneider and Gilbert[8] and Host[27] each made duplicate tests on two normals and found that the maximal differences between coincident points on the two curves exceeded 0.05 per cent in every case. Glassberg[17] found differences of 0.05 per cent or more in three out of five duplicate curves. Nielsen[42], on the other hand, obtained fair agreement between the two curves in seven persons on a mixed diet and three almost identical curves in an individual on a uniform diet. Since the subjects reported by the other authors were on a mixed diet during the intervals between the tests, the question naturally arose as to whether the diet was responsible for the disparity in the curves. Horsters[26] stated that he obtained consistent curves after a glucose meal in non-diabetics on a standardized diet, but his figures, given in only two cases, do not well substantiate his claim. Soisalo[51] carried out duplicate glucose tolerance tests on seventeen healthy young adults who were placed on an identical dietetic ration for two days prior to each test. He obtained good checks in nine cases but found marked differences between the two curves in the other eight, and concluded that the variations in duplicate curves were as great after a standardized diet as otherwise.

SUGGESTED VARIATIONS OF THE ORAL TEST

Attempts to improve the test considered above as standard by using two doses of glucose one to two hours apart (Traugott-Staub method), and by substituting starch or a mixed meal as the testing substance have proven disappointing. Malmros and Julesz[31] recently demonstrated that many normals show a diabetic type of response to the Traugott-Staub test, and concluded that this method yields no more information than the standard test with a single dose of glucose. Rowe and Rogers[49] showed that glucose is more reliable as a testing substance in detecting mild diabetes than starch or mixed meals. Gray[19]

collected the blood sugar curves of seventeen mild diabetics after a mixed meal containing at least 40 gms. carbohydrate and found a perfectly normal average curve.*

INFLUENCE OF GASTRIC EMPTYING AND INTESTINAL ABSORPTION ON GLUCOSE TOLERANCE CURVES

Is the frequent lack of parallelism in repeated curves after the ingestion of glucose by the same normal individual under identical experimental conditions necessarily due to fluctuation in the capacity to utilize carbohydrate, or may it be due, in part at least, to irregularities in absorption? Are the abnormal curves often obtained in non-diabetic endocrinal disease, carcinoma, et cetera, and the all too common normal curve obtained in diabetes necessarily due to alterations in carbohydrate metabolism, or may they, too, result from abnormalities in absorpton?

The possibility of alterations in the curve through variations in absorption has been considered by many workers, but usually has been perfunctorily dismissed. The problem is a difficult one in man because the rate of absorption of glucose from the gastro-intestinal tract cannot be determined directly. Considerable indirect evidence may be obtained, however, from a study of the emptying time of the stomach. It is generally agreed that absorption of glucose from the stomach is negligible, and that most, if not all, that is ingested passes through the pylorus and is absorbed in the small intestine. The following work is cited to show (1) that there are marked variations in the evacuation time of the stomach among normal individuals, and (2) that there are corresponding changes in the shape of the blood sugar curves, both in health and disease.

Kasabach[32] followed fluoroscopically at 15 minute intervals, the passage of a mixture consisting of 1 tablespoonful of skiabaryt in 500 cc. of water out of the stomachs of fifty healthy university

* Since this manuscript was prepared, Exton and Rose (Am. Jour. Clin. Path., **4**: 381–400, 1934) have published promising preliminary data on a new modification of the Traugott-Staub test. Since the fundamental principle of the two tests is similar, more extensive investigation may well show the same drawbacks in the new as in the original method.

students. Twenty similar observations were carried out using 50 per cent glucose in place of water. The variability of the evacuation time of the stomach in the selected group of normals is evident from the figures in table 2 taken from Kasabach's paper:

Results at first glance contradictory to the foregoing have been reported by Malmros.* He aspirated the stomachs of two healthy young adults one and a half and two hours respectively after the ingestion of 1 gram of glucose per kilo, recovered a negligible quantity in each case and found that the blood sugar had already returned to normal and was not affected by the aspiration. The uniform results in these two cases do not invalidate the variability reported by other observers in longer series. Even these two individuals showed considerable gastric residue together with changes in the blood sugar curve when larger doses of glucose were administered.

TABLE 2

TESTING SUBSTANCE	EMPTYING TIME OF THE STOMACH IN MINUTES						TOTAL CASES
	30	45	60	75	90	120	
	per cent	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*	
500 cc. water—½ oz. skiabaryt.....	10	28	36	14	6	6	50
500 cc. glucose—½ oz. skiabaryt.....	5	30	35	10	10	10	20

To a series of rats of about the same age and weight, fasting sufficiently long to insure an empty gastrointestinal tract, Cori[11] gave accurately measured quantities of glucose by stomach tube in doses ranging between 0.44 to 1.45 grams per 100 grams body weight (4.4 to 14.5 gram/Kg.). Some were killed at the end of an hour, others at two hours, the remainder at three hours, the gastrointestinal tracts removed and the contents analyzed for glucose. Cori's

* Wishnofsky (Jour. Lab. and Clin. Med., **19:** 1286–1292. 1934) has recently performed duplicate oral tolerance tests with different quantities of glucose on fourteen diabetic patients. He has attempted to gauge the rate of absorption from differences in the rise in blood sugar, assuming the absorption is continuing as long as the blood sugar is rising and is completed as soon as the blood sugar begins to fall. Applying this interpretation to his results in cases 10, 12 and 13, one finds that the absorption of 150 grams was completed more rapidly on one occasion than was 75 grams on the other. In our opinion, this method of determining absorption rate is unreliable and misleading, since it depends upon the assumption that the rate of removal of glucose from the blood stream is constant from time to time in a given diabetic, which is contrary to everyday clinical experience.

results showed a uniform absorption during the first and second hours and a slight falling off in the third hour. Because of the marked differences in dosage per unit body weight, Cori's conclusions cannot be applied to the human glucose tolerance test. Since Pearce, Osgood, and Polansky,[46] using smaller doses, did not find uniform absorption, a second series of experiments[10] was carried out using an average dose of 7.17 gram/Kg., which was slightly in excess of the average amount absorbed in three hours (6.84 gram/Kg.) Even in these experiments, conditions were not analogous to those in humans, since calculations on the assumption of uniform absorption show an average of 2.39 gram/Kg. present in the gastrointestinal tract at the beginning of the third hour. Magee[38] stated that both he and his co-workers and Cori have had to exclude from the averages numerous experiments in which little or no absorption took place because of diarrhea or pylorospasm. Burgett, Moore, and Lloyd[9] have recently repeated Cori's work, using a dose of 1 gram glucose throughout and found absorption rates ranging between 0.35 gram and 0.8 gram per hour. The absorption was most rapid in the first thirty minutes and fell off decidedly in the second hour. In a series of eight male dogs, killed one hour after the administration of glucose by stomach tube, Trimble, Carey and Maddock[54] found an absorption rate varying from 0.74 to 1.33 grams/Kg. per hour.

Beeler, Bryan, Cathcart and Fitz[5] administered 100 gms. glucose in 500 cc. water to four normal, one obese and four diabetic individuals, without producing nausea. One hour later the stomach contents were aspirated through a Rehfuss tube, and amounts ranging from 22.2 to 68 gms. of glucose were recovered. Since Rehfuss, Bergeim, and Hawk had shown that the stomach can be almost completely emptied through the small tube, the marked differences in the amount of glucose recovered were attributed to individual variations in the emptying time of the stomach. Bennett and Ryle,[6] Baird, Campbell and Hern[3] and Apperly and Semmens[1] administered a pint of thin gruel made from 1 ounce of oatmeal to twenty healthy young adults, withdrew fractional specimens every 15 minutes, tested for the presence of starch, and considered the stomach empty when the addition of iodine no longer resulted in a blue color. They found that complete evacuation of the stomach contents may take place at any point from one-half to four hours.

Thus, by all of the foregoing methods, marked variations in gastric emptying time have been found among normal individuals. That even greater discrepancies occur with organic lesions of the stomach, and in debilitating disease scarcely needs comment.

The influence of the rate of glucose into the duodenum upon the blood sugar has been studied by Hale-White and Payne.[20]* They passed a tube into the duodenum of a healthy young adult on two different occasions, injected 50 gms. glucose in 500 cc. water at a uniform rate of 5 cc. per minute on one day, and as rapidly as possible without causing discomfort on the other. They took capillary specimens on each occasion at five to ten minute intervals for a period of two hours and found that a hyperglycemia was maintained as long as sugar was being introduced into the duodenum, but that the blood sugar level fell off rapidly after the termination of the injection. Their results, graphically represented in chart 1, well illustrate the influence of the emptying time of the stomach on the blood sugar curve. In accord with their findings is the clinical observation that patients with benign pyloric stenosis show an abnormally prolonged hyperglycemia after the ingestion of glucose. (Gravila and Sparchez,[18] Watson,[55] Meyer.[40]) In patients with roentgenographic evidence of rapid gastric evacuation, an abnormally high blood sugar was found one-half hour after the ingestion of glucose, followed by a precipitate fall to the fasting level,[55, 40]. A case of pyloric obstruction reported by Meyer showed striking differences in the oral glucose tolerance curve before and after operation (see chart 1). Roth and Ernest[48] studied the relationship

* Since this manuscript was completed, Magers (Jour. Lab. and Clin. Med., **19:** 608–611. 1934) has elaborated upon the work of Hale-White and Payne in a paper entitled: "A comparison of blood sugar curves when glucose is given orally and intraduodenally." The blood sugar curves after the ingestion of 50 grams glucose in 333 cc. water were compared with those obtained on the same individual after the injection of a similar quantity through a Rehfuss tube. The injection was not made until bile stained alkaline fluid could be aspirated through the tube. The tip was then considered to be in the duodenum but its position was not verified by fluoroscope. Since a bile stained alkaline fluid not infrequently regurgitates into the stomach, there is reasonable doubt that the Rehfuss tip was actually in the duodenum. Furthermore, the fact that the entire volume could be injected in as short a time as 3 minutes throws doubt that it actually passed directly into the duodenum. Even so, the blood sugar level 2 hours after the ingestion of glucose was abnormally high in four of the seven non-diabetics tested, whereas it was above normal in only one when the glucose was injected through the tube.

between the rate of evacuation of the stomach by X-ray and the initial rise in respiratory quotient after a mixed meal containing 235 grams carbohydrate. Two out of three normals showed a distinct rise in respiratory quotient at the end of one hour; a case with accelerated gastric emptying showed a marked increase at that time, whereas in pyloric stenosis the first definite rise occurred at the end of the third hour. John[40] and Hale-White and Payne[20] observed that patients who became nauseated during the course of a glucose tolerance test showed a coincident dip in the blood sugar curve, and a secondary rise as soon as the nausea

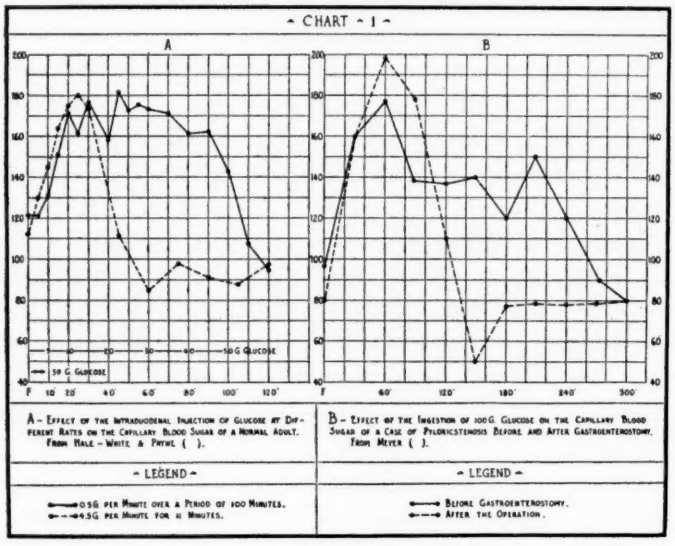
CHART 1
A
B
50 G GLUCOSE
A – EFFECT OF THE INTRADUODENAL INJECTION OF GLUCOSE AT DIFFERENT RATES ON THE CAPILLARY BLOOD SUGAR OF A NORMAL ADULT. FROM HALE – WHITE & PAYNE ( ).
B – EFFECT OF THE INGESTION OF 100 G. GLUCOSE ON THE CAPILLARY BLOOD SUGAR OF A CASE OF PYLORICSTENOSIS BEFORE AND AFTER GASTROENTEROSTOMY. FROM MEYER ( ).
LEGEND
0.5G PER MINUTE OVER A PERIOD OF 100 MINUTES.
0.5G PER MINUTE FOR 11 MINUTES.
LEGEND
BEFORE GASTROENTEROSTOMY.
AFTER THE OPERATION.

CHART 1

disappeared, and attributed the changes in blood sugar to pylorospasm associated with the nausea. Kisch[35] found a rough parallelism between the degree of cardiac decompensation, the rate of gastric evacuation, and the shape of the blood sugar curve. Alterations in the emptying time of the stomach produced in animals by the addition of olive oil to a starch meal[25] and by the administration of opiates at the time of the glucose meal,[36] were accompanied by corresponding changes in the blood sugar curve. Satake and Fujii[50] introduced glucose directly into the stomachs of dogs previously rendered insensitive by bilateral posterior nerve

root section, took nearly simultaneous specimens from the portal and ear veins, and found that the portal and systemic blood sugar curves were parallel. Since the same irregularities were present in both curves, the authors concluded that absorption factors were responsible.

SUMMARY

The literature on oral glucose tolerance test has been reviewed and the inadequacies of the test re-emphasized. Curves similar to those obtained in diabetes mellitus have been reported in a wide variety of diseases in which there was no clinical evidence of a coexisting diabetes. Conversely, "normal" and "borderline" curves have been found not infrequently in undoubted cases of diabetes mellitus. Duplicate tests in normal individuals under uniform conditions of experiment have commonly resulted in widely divergent curves.

Since marked variations in the evacuation time of the stomach have been found in normal individuals, and corresponding changes in the shape of the blood sugar curve have been repeatedly demonstrated, it would seem that these points may well explain the discrepancies to which we have referred.

REFERENCES

(1) Apperly, F. L. and Semmons, K. M.: Fractional test meal in normal students, comparison of results with those of other observers. Med. Jour. Australia, **2:** 237–239. 1928.

(2) Archer, B. H.: Sugar tolerance in arthritis. Arch. Int. Med., **44:** 37–46. 1929; **44:** 238–243. 1929.

(3) Baird, M. Mc., Campbell, J. M. H., and Hern, J. R. B.: Gastric secretion, physique and physical fitness. Guy's Hosp. Rep., **74:** 339–353. 1924.

(4) Bang, I.: Der Blutzucker. Wiesbaden: J. F. Bergmann, 1913, pp. 162.

(5) Beeler, C., Bryan, A. W., Cathcart, E. P. and Fitz, R.: An improved alimentary glucose tolerance test. Jour. Metab. Research, **1:** 549–560. 1922.

(6) Bennett, T. I. and Ryle, J. A.: Studies in gastric secretion; study of normal gastric function based on investigation of 100 healthy men by means of fractional method of gastric analysis. Guy's Hosp. Rep., **71:** 286–318. 1921.

(7) BIERMER, H.: Ueber die Blutzuckerkurve des Magen-Darmkarzinoms und ihre diagnostische Bedeutung. Deut. Med. Wochenschr., **50:** 597–599. 1924.

(8) BOCK, J. C., GILBERT, M. AND SCHNEIDER, H.: Blood sugar studies. Jour. Biol. Chem., **67:** 629–645. 1926.

(9) BURGETT, G. E., MOORE, P. AND LLOYD, R.: Relative absorption rates of dextrose and levulose. Am. Jour. Physiol., **101:** 565–569. 1932.

(10) CORI, C. F., CORI, G. T. AND GOLTZ, H. L.: On the mechanism of glucose absorption from the intestinal tract. Proc. Soc. Exper. Biol. and Med., **26:** 433–436. 1929.

(11) CORI, C. F.: Rate of absorption of hexoses and pentoses from the intestinal tract. Jour. Biol. Chem., **66:** 691–715. 1925.

(12) CUMMINGS, R. AND PINESS, G.: Study of blood sugar. Arch. Int. Med., **19:** 777–785. 1917.

(13) DENIS, W., AUB, J. C. AND MINOT, A. S.: Blood sugar in hyperthyroidism. Arch. Int. Med., **20:** 964–972. 1917.

(14) FRIEDENWALD, J. AND GROVE, G. H.: Blood sugar tolerance test as an aid in the diagnosis of gastro-intestinal cancer. Am. Jour. Med. Soc., **163:** 33–40. 1922.

(15) GARDINER-HILL, H., BRETT, P. C. AND SMITH, F.: Carbohydrate tolerance in myxedema. Quart. Jour. Med., **18:** 327–334. 1925.

(16) GLASSBERG, B. Y.: Arteriovenous difference in blood sugar content. Arch. Int. Med., **46:** 605–609. 1930.

(17) GLASSBERG, B. Y.: Diagnostic value of the sugar tolerance curve in endocrinopathies. Arch. Int. Med., **46:** 984–987. 1930.

(18) GRAVILA, I. AND SPARCHEZ, T.: L'épreuve de l'hyperglycémie provoquée dans les maladies du tube digestif. C. R. Soc. d. Biol., **96:** 61–63. 1927.

(19) GRAY, H.: Blood sugar standards; normal and diabetic persons. Arch. Int. Med., **31:** 241–262. 1923.

(20) HALE-WHITE, R. AND PAYNE, W. W.: Dextrose tolerance curve in health. Quart. Jour. Med., **19:** 393–410. 1926.

(21) HAMMAN, L. AND HIRSCHMAN, I. I.: Studies on blood sugar. Arch. Int. Med., **20:** 761–808. 1917.

(22) HOLCOMB, B.: Study of blood sugar curves before and after thyroidectomy. Endocrin., **13:** 467–476. 1929.

(23) HOLSTI, O.: Studies concerning variations of blood sugar reaction in disease. Acta Med. Scand., **66:** 443–460. 1927.

(24) HOPKINS, A. H.: Studies in the concentration of blood sugar in health and disease determined by Bang's micromethod. Am. Jour. Med. Sc., **149:** 254–267. 1915.

(25) HORIUCHI, T.: Relation between absorption of carbohydrate and blood sugar. Jour. Biochem., **4:** 1–32. 1924.

(26) HORSTERS, H.: Ueber die individuelle Konstanz der Blutzuckerkurven biem Menschen. Ztschr. f. d. ges. exper. Med., **83:** 72–91. 1932.

(27) HOST, H. F.: Urine sugar and its relation to blood sugar. Jour. Metab. Research, **4:** 316–414. 1923.

(28) JACOBSEN, A. T. B.: Untersuchungen ueber den Einfluss verschiedener Nahrungsmittel auf den Blutzucker bei normalen, zuckerkranken und graviden Personen. Biochem. Ztschr., **56:** 471–494. 1913.

(29) JANNEY, N. W. AND ISAACSON, V. I.: Blood sugar in endocrine disease. Arch. Int. Med., **22:** 160–173. 1918.

(30) JOHN, H. J.: Glucose tolerance and its value on diagnosis. Jour. Metab. Research, **1:** 497–548. 1922; **4:** 255–313. 1923.

(31) JULESZ, M.: Die Bewertung der doppelten Glucosebelastungsversuche. Ztschr. f. d. ges. exper. Med., **79:** 153–163. 1931.

(32) KASABACH, H. H.: Effect of ingestion of water and of dextrose solution on emptying time of normal stomach. Arch. Int. Med., **48:** 1237–1240. 1931.

(33) KASANIN, J. AND GRABFIELD, G. P.: Blood sugar curves in epidemic encephalitis. Arch. Int. Med., **37:** 102–109. 1926.

(34) KERN, R. A. AND JONES, L.: Sugar tolerance testing. Jour. Am. Med. Assn., **81:** 1439–1441. 1923.

(35) KISCH, B.: Beobachtungen ueber das Verhalten der glykaemischen Reaktion und der Magenmotilitaet bei Kranken mit Kreislaufsinsuffizienz. Ztschr. f. d. ges. exper. Med., **50:** 218–237. 1926.

(36) KLERCKER, KJ. O.: Untersuchugen ueber die Einwirkung der Opiumalkaloide auf gewisse Hyperglykaemien. Biochem. Ztschr., **62:** 11–48. 1914.

(37) LENNOX, M. G.: Repeated blood sugar curves in non-diabetic subjects. Jour. Clin. Invest., **4:** 331–352. 1927.

(38) MAGEE, H. C.: Rôle of small intestine in nutrition. Physiol. Rev., **10:** 473–505. 1930.

(39) MALMROS, H.: Study of glycosuria, with special reference to interpretation of incidental finding of positive reduction test. Acta Med. Scand., Supp. no. **27:** 1–309. 1928.

(40) MEYER, P. F.: Zur peroralen Zuckerbelastung. Ztschr. f. klin. Med., **121:** 455–464. 1932.

(41) MOSENTHAL, H. O.: Interpretation of sugar tolerance tests; common occurrence of renal glycosuria. Med. Clin. N. Amer., **9:** 549–574. 1925.

(42) NIELSEN, O. J.: On oscillations of blood sugar values within brief periods and blood sugar curve on uniform ingestion of glucose. Biochem. Jour., **22:** 1490–1498. 1928.

(43) NIEMEYER, R.: Ueber Blutzuckerreaktion. Ztschr. f. klin. Med., **98:** 132–145. 1924.

(44) Olmstead, W. H. and Gay, L. P.: Study of blood sugar curves following a standardized glucose meal. Arch. Int. Med., **29:** 384–399. 1922.

(45) Pemberton, R. and Foster, G. L.: Studies on arthritis in army based on 400 cases. Arch. Int. Med., **25:** 243–282. 1920.

(46) Pierce, H. B., Osgood, H. S. and Polansky, J. B.: Absorption of glucose from alimentary tract of rats deprived of vitamin B. complex. Proc. Soc. Exper. Biol. and Med., **26:** 347. 1929.

(47) Ralli, E. P. and Shannon, J.: Study of 5-hour dextrose tolerance curve in treated diabetic patients. Am. Jour. Med. Sc., **182:** 395–405. 1931.

(48) Roth, N. and Ernst, Z.: Einfluss der Magenfunktion auf den Kohlenhydratstoffwechsel. Ztschr. f. klin. Med., **93:** 417–423. 1922.

(49) Rowe, A. H. and Rogers, H.: Value of carbohydrate tolerance tests in diagnosis of diabetes mellitus. Calif. and West. Med., **26:** 64–70. 1927.

(50) Satake, Y. and Fugii, I.: Resorption of glucose into portal vein. Tohoku Jour. Exper. Med., **7:** 522–534. 1926.

(51) Soisalo, P.: On the blood sugar curve in healthy persons. Acta Med. Scand., Supp. no. **34:** 184–187. 1930.

(52) Strouse, S.: Observations on alimentary hyperglycemia. Arch. Int. Med., **26:** 759–767. 1920.

(53) Traut, E. F.: Glucose tolerance in arthritis. Jour. Metab. Research, **7–8:** 187–193. 1926.

(54) Trimble, H. C., Carey, H. W. and Maddock, S. J.: The rate of absorption of glucose from the gastrointestinal tract of the dog. Jour. Biol. Chem., **100:** 125–138. 1933.

(55) Watson, E. M.: Factors in interpretation of certain anomalous blood sugar curves. Canad. Med. Assn. Jour., **17:** 1036–1040. 1927.

(56) Williams, J. R. and Humphreys, E. M.: Observations on tolerance and rate of utilization of glucose in series of individuals exhibiting various degrees of diabetes mellitus. Arch. Int. Med., **23:** 559–81. 1919.

(57) Wishnofsky, M.: Dextrose tolerance test; its use in determining severity of diabetes mellitus. Arch. Int. Med., **42:** 443–452. 1928.

A SIMPLE METHOD OF SUPPLYING CARBON DIOXIDE IN JARS FOR BACTERIOLOGIC CULTURES

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In July, 1934, McLeod et al. called attention to the fact that carbon dioxide has a stimulating effect on the growth of *Neisseria gonorrhoeae*. Previously, Huddleson had used carbon dioxide to advantage in culturing *Brucella abortus*. The value of McLeod's method of culturing *Neisseria gonorrhoeae* has been confirmed by Leahy and Carpenter, who have used a method similar to that described by Huddleson for introducing carbon dioxide into the jar in which the cultures are incubated. The apparatus necessary for Huddleson's method consists of a cylinder of carbon dioxide, a reducing valve, a graduated receptacle for collecting the carbon dioxide, and suitable connections with a water supply for forcing the carbon dioxide from the measuring cylinder into the culture jar.

METHOD

The method to be described is very simple and requires no special apparatus. The carbon dioxide is derived from sodium bicarbonate which has been mixed with sulphuric acid. Two solutions are prepared: one, a molar solution of sodium bicarbonate, which is made by dissolving 84 grams of sodium bicarbonate in water and making the volume up to one liter; the other, a solution of sulphuric acid, which is made by diluting concentrated sulphuric acid so that 1 cc. of acid is added to 29 cc. of water. The acid so made is sufficient to react with the bicarbonate solution part for part and still leave a slight excess of acid. Sulphuric acid, being non-volatile, does not affect the cultures. Each cubic centimeter of the bicarbonate solution should furnish 22.4 cc. of carbon dioxide.

The picture (fig. 1) shows how the jar is used. An ordinary 3 quart museum jar, like the one in the illustration, has proved very satisfactory. A rubber ring is used for a seal, but no other precautions have to be taken to prevent loss of carbon dioxide from the jar. The plates that are to be incubated are placed in the jar, as shown; then, a sufficient quantity of the bicarbonate solu-

tion to produce approximately a 10 per cent concentration of carbon dioxide within the jar is placed in the small wide mouth bottle which is similar to the one shown in the picture. The cover is put in place and an amount of the sulphuric acid solution equal to the amount of bicarbonate solution that is employed is added with a pipet, through a hole in the cover. The stopper is restored to the hole as promptly as possible, and the jar is placed in the incubator.

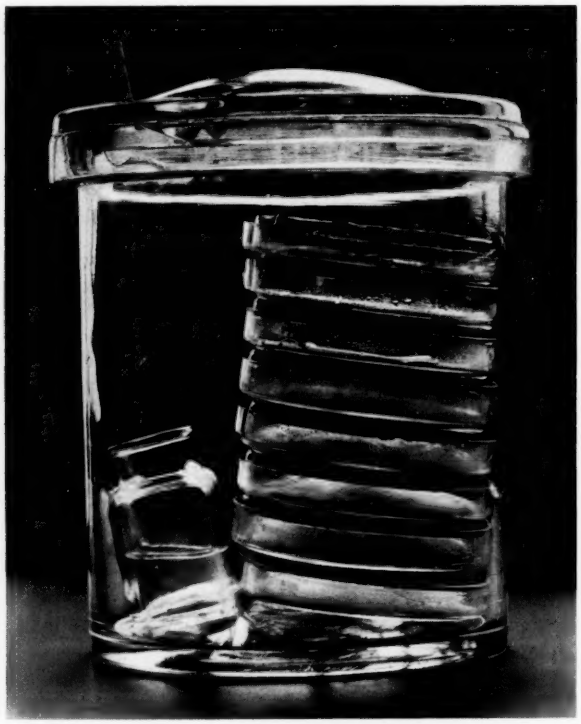

FIG. 1. CARBON DIOXIDE JAR

Excellent growth of *Neisseria gonorrhoeae* has been obtained in twenty-four hours with this method. No difficulty has been experienced so far, in a limited number of cases, in culturing *Neisseria gonorrhoeae* in cases in which it can be demonstrated in smears. It has been possible to culture the organism in cases in which the smear was negative or doubtful. It appears that carbon dioxide is very helpful in promoting growth and that *Neisseria gonorrhoeae* can be grown as readily in an atmosphere of

carbon dioxide as can streptococci on the ordinary blood agar plate under the usual conditions. It is believed that the method of culturing and identifying *Neisseria gonorrhoeae* by the oxidase reaction, as described by McLeod, is adapted to routine clinical use, and that a simple method of getting the proper amount of carbon dioxide, such as is here described, will do much to encourage its use.

In two instances it was possible to secure a profuse growth of *Neisseria intracellularis* (the meningococcus) from spinal fluids in less than twenty-four hours by using the same medium as for *Neisseria gonorrhoeae* and by incubating in the jar as described above. Evidently carbon dioxide has a markedly stimulating effect upon this organism also. In the two cases in which *Neisseria intracellularis* was found in the spinal fluid, it was also possible to demonstrate it with ease by culturing from the nasopharynx. It seems probable that this method would be an excellent one for the detection of meningococcus carriers.

REFERENCES

(1) Huddleson, I. F.: Brucella infections in animals and man. New York, Oxford University Press, p. 11, 1934.

(2) Leahy, Alice D. and Carpenter, C. M.: The isolation of Neisseria gonorrhoeae. Jour. Bacteriol. **29:** 36. 1935.

(3) McLeod, J. W., Coates, J. C., Happold, F. C., Priestley, D. P. and Wheatley, B.: Cultivation of the gonococcus as a method in the diagnosis of gonorrhoea with special reference to the oxydase reaction and to the value of air reinforced in its carbon dioxide content. Jour. Path. and Bacteriol. **39:** 221–231. 1934.

REFORM IN COUNTY GOVERNMENT AND THE CORONER'S OFFICE

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In 1900 Galveston, Texas, adopted a commission plan of municipal government as a form of administration that would best enable the city to overcome the havoc wrought by a tidal wave. A still further concentration of administrative authority and responsibility was brought about by the city manager plan put into effect by Dayton, Ohio, in 1914. Since then one or the other of these modernized forms of city government has been adopted by a constantly increasing number of American municipalities. Their efficiency has been amply demonstrated wherever they have been permitted to operate unhampered by corrupt local partisan politics.

THE COUNTY

It was but natural that the success of the commission or manager form of municipal government should lead to suggestions for the adaptation of a similar governmental structure to the county, when the depression forced this unit in most of our states to the brink of insolvency and bankruptcy. The county itself, as a geographic subdivision of the state, and its offices, as administrative agencies, had become archaic. They belong to an outworn stage of our civilization, when man was fettered to his immediate environment by the slowness of his means of transportation.

Although half-hearted efforts had been made during the past decade to concentrate greater power and responsibility in the county board, a definite trend toward a modernized system, now possible in a number of states, did not become evident until 1929 or 1930.

The newer trends provide either for one of several options permissible under a revised state constitution or for county home-

rule. Under the optional system a county may, by referendum vote, adopt a county executive or county manager form of administration. Under the home-rule plan the county adopts a charter that best fits its own individual needs, subject, of course, to the provisions of the state constitution.

Counties differ greatly in population, in valuation of taxable property, and in the problems that have to be met by government. Considerable latitude should, therefore, be allowed the individual county in order that it may select the form of government best suited to its needs. In 1930 the Committee on County Government of the National Municipal League drafted a model county manager law.[2] In 1932 this committee presented a draft of a model state constitution,[3] under which any one of several alternative forms of county government may be adopted.

REORGANIZATION OF COUNTY BUSINESS

The newer proposals contemplate not only the elimination of many elective county offices and the shortening of the ballot, but departmentalization and modernization of the county's business and administrative offices under appointive department heads. Most of the county's administrative functions relate to the county itself and fall naturally into departments, such as finance, records, public health and welfare, highways, et ectera. Some county functions do not relate to the county itself but to the state as a whole. They have to do with the enforcement of state laws within the county. These are the duties that under the present system fall upon the sheriff, the prosecutor, and the coroner.

Students of political science find it difficult to place these in a modernized county governmental structure. Most hold that these officers, like the other county officials, should be appointive rather than elective, but the propriety of having them appointed by the county board or the county manager is questioned. The functions of these officials fall into what might be considered a county department of administration of criminal justice. It has been suggested that the county prosecutor should be appointed by the attorney-general of the state, the sheriff and coroner by the governor. With a well organized and efficient state constabulary,

the sheriff loses his importance as a county official. He becomes a court bailiff and keeper of the county jail, neither of which functions requires a special official. The office of coroner, in its present form, has become even more useless.

Appointment of county officials and organization of the county's business into departments would solve many but not all of the county's problems. Some of the latter are dependent upon the size of the county. The size of counties was influenced by the limitations of transportation in the horse and buggy days when county boundaries were established. Although there is much variation in the area of counties, the usual size of a rural county in most of the states is from 400 to 700 square miles.

With modern transportation and good highways, a much larger unit of territory than the present average county can be well administered by a single set of officials. Bromage[1] thinks the county under modern conditions should have a minimum area of 2000 square miles. Territorial consolidation of counties into units of such size would greatly facilitate efficient administration. Local pride and the influence of the hordes of county officials who would be thrown out of office will probably effectively prevent the territorial consolidation of counties into larger units.

Territorial consolidation of counties may be far distant in the future, but functional consolidation is feasible. In judicial administration it has been a fact for many years in many states. The circuit court derives its name from the fact that the judge made the circuit of two or more counties for the purpose of holding court. In the business administration of counties, consolidation has also made headway. In many states counties may unite in the maintenance of tuberculosis sanitoria, other hospitals, almshouses, and jails. Consolidation of the public health work of counties has made it possible for such larger combined units to employ full-time public health officials. Many states have incorporated county highways into the state highway system.

THE CORONER AS A COUNTY OFFICIAL

The coroner is a county official. It was natural that the office which was transplanted from England to the Colonies should have

been, not the office of coroner of the city of London or that of borough coroner, but that of rural county coroner. In the United States his jurisdiction is limited to the county in which he is elected, but his relations are to the laws of the state rather than to the business of the county as such.

The defects of the coroner system as it operates in the greater part of the United States have been frequently enumerated and need not be recounted here. As an agency for the application of medical science to the needs of law and justice the office of coroner is a failure. Under it medicine has little opportunity to render to government the service that the profession is capable of rendering. Antiquated laws, the elective character of the office, the short tenure, the lack of professional qualifications, and inadequate facilities combine to produce a system in which modern scientific medicine has no place.

With the establishment of orderly government society found it necessary to set up an agency that must take official cognizance of certain classes of deaths. These fall into the four main classes of criminal homicide or murder, suicide, accident, and sudden death when the deceased has not been attended by a physician. The need for official investigation is evident. In England and its colonies and in the United States, with the exception of a few localities, the investigating agency is the office of coroner. This is a hybrid institution that must rely upon medical science for the determination of the cause of death, if the cause is to be accurately determined. In the inquest the coroner performs a magisterial or quasi-judicial function that should require knowledge of the law. He conducts an investigation that could be better done by the police and that must be repeated by the prosecutor if there is an element of criminality or negligence. When there is no such element the necessary investigation is purely medical and there is no reason for such an office as that of coroner.

THE MEDICAL EXAMINER

The citizens of Massachusetts early recognized the defects of the coroner system and abolished it in 1877. The coroner was replaced by an appointive official, known as a medical examiner,

with purely medical duties. He makes his investigation uninfluenced by political considerations and unhampered by a petty politician of coroner type. If the medical examination reveals no suspicious circumstances, the medical examiner authorizes or issues a death certificate and the case is closed. If the examination brings to light any evidence of foul play or negligence, the medical examiner reports his findings with all the facts ascertained by him to the prosecuting attorney. The latter, with the aid of the police, can then undertake an investigation that has not already been muddled and befuddled by an inquest such as the average coroner holds.

The medical examiner system became effective in New York City in 1918 and in Essex County (Newark), New Jersey, in 1927. In these jurisdictions and in Suffolk County (Boston), Massachusetts, the medical examiner system has proved its superiority over the coroner system. The medical examiners are experts in medicolegal pathology. They are appointive officials and have served continuously, either by reappointment or under civil service. This results in a much higher type of work than is possible with an elective coroner. The laws under which they work are more modern than those relating to the office of coroner and define precisely the duties and authority of the medical examiner. Under the medical examiner system medicine has had an opportunity to demonstrate the service that it can render to law and justice.

In populous counties or large cities the governmental agency that must investigate deaths has important duties and a large volume of work to perform. In rural counties the office of coroner sinks into insignificance. Work of the poorest sort is all that the inhabitants of such counties can expect. Many sparsely settled counties have less than a score of coroner's cases in the course of a year. But the inhabitants of such counties are just as much entitled to full and impartial justice as are the citizens of a densely populated county, where the number of coroner's cases runs into the thousands. For the rural county no very great improvement seems possible under the present system of county government.

The superiority of the medical examiner system over the coroner system in populous jurisdictions has been thoroughly established. In less densely populated areas the medical examiner system, as it has thus far been worked out in such areas, is better than the coroner system but is not so good as it should be. When Massachusetts replaced the office of coroner by that of medical examiner in 1877, the change became effective throughout the state. Two full-time salaried medical examiners were provided for Suffolk County, but in other counties as many medical examiners working on a fee basis were to be appointed by the governor as the county commissioners deemed necessary. The number of examiners in outlying counties varies from one to eleven per county, the total number outside of Suffolk County being seventy-one. In that they are appointed and are physicians, the system is an improvement over the elective coroner system. Massachusetts was still under the influence of the horse and buggy tradition at the time it adopted its state-wide medical examiner system.

A STATE-WIDE MEDICAL EXAMINER SYSTEM

Although the number of deaths requiring medicolegal investigation in rural counties is small, it should be possible to devise a system that would insure efficient investigation of such deaths. The coroner system has demonstrated its inefficacy. It is time to replace it by a system that at one and the same time brings to bear a fuller use of modern medical knowledge and utilizes the advantages of modern transportation. Such a system must be state-wide in its application, if sparsely settled counties are to receive a quality of service that they cannot afford but should have.

The actual territorial consolidation of several counties into larger units appears to be out of the question. But a functional consolidation of two or more counties into a single medical examiner district should be feasible if a revised state constitution will permit such an arrangement. The size of such units should be determined by population, areas, population density, the extent to which the population is condensed into cities, and the

highway system. A county with a large metropolitan population should constitute a single district. In the more rural parts of the state two or more less densely populated counties could be grouped with a more densely populated one, preferably one with a fairly large city. Each district should have an area of 2000 to 3000 square miles, which is held to be the desirable size of a unit of county administration. The cost could be prorated among the counties of the district according to the volume of work of each. The maximum distance from a central medical examiner headquarters would not exceed 50 to 75 miles, a distance easily covered by automobile.

If the medical examiners in such a system are placed on salary and are appointed by the governor of the state or by a state civil service commission and if they serve under civil service, it should be possible to obtain the services of competently trained pathologists. In districts with a limited volume of work, a hospital pathologist might serve as medical examiner on a half-time basis. Such a state-wide district medical examiner system should be capped by a state-supported medicolegal institute of the kind recommended by the American Medical Association and the American Bar Association. To such an institute the district medical examiners of the state could submit materials requiring toxicologic, histologic or other laboratory investigation. What is here proposed would place forensic medicine in the United States on a plane equal to that of this discipline in Europe. It would make available to society through a governmental agency a quality of scientific service on a par with that of European medicolegal institutes.

If the movements now under way in many parts of the country, movements having as their aim the modernization of state constitutions and the reorganization of county government, bear fruit, it should be possible to develop such a medicolegal system as has been suggested.' But the medical profession must take an alert and intelligent interest in what is going on. The physician, as a citizen, should take a leading part in movements whose aim is the betterment of the local governmental unit in which he lives. As a physician, he should take especial interest in pro-

posals that require medical activity for their success. The physician, engrossed in his own professional activities, is prone to let agencies other than his own professional organizations propose and put into effect measures that relate directly to medicine, measures in whose promulgation he has had no part, usually through his own lack of interest. If physicians displayed greater activity in moulding public opinion and in guiding legislation, there might be less exploitation of the profession, less fear of "state medicine," and fewer commercially controlled health insurance schemes. And in time American medicine might have reason to be proud of its achievements in the field of forensic medicine.

SUMMARY

There is evident in many parts of the country a trend toward the reform and reorganization of the American system of county government.

In many states the proposals for modernizing county government require revision of the state constitution. A strong movement in this direction is also evident.

Such proposals, if they become effective, present an opportunity for the development of a modern medicolegal system.

Such a system should be one that discards the coroner's inquest and makes use of the services of a medical examiner.

The system should be state-wide in its application. In rural districts it should disregard county lines and should consist of districts composed of two or more counties.

The medical examiners should be competently trained pathologists. They should be appointed and should serve under civil service. They should be on a full-time or part-time salary basis, depending upon the volume of work of the district.

The state-wide district medical examiner system should be centered in a state-supported medicolegal institute to which the examiners of the state could submit materials requiring scientific investigation.

If the medical profession is not to be forced into doing things that are harmful to the best interests of the profession, the latter

must take an active part in the promulgation of measures that require medical activity.

The technical character of the duties of the office of coroner would appear to make the functioning of this office important perhaps only to members of the medical and legal professions. Its importance in the administration of criminal justice and in the adjudication of claims for accident insurance and workmen's compensation should make reform of the antiquated office of coroner a matter of concern to every citizen interested in better government.

REFERENCES

(1) Bromage, Arthur W.: American county government. New York: Sears Publishing Company, p. 207, 1933.

(2) Committee on County Government, National Municipal League: A model county manager law. Nat. Municipal Rev., **19:** 565, 1930.

(3) Committee on County Government, National Municipal League: Recommendations of the committee on county government as to provisions on local government for the model state constitution. Nat. Municipal Rev., **21:** 540, 1932.

STANDARDIZING SICKLE CELL METHOD AND EVIDENCE OF SICKLE CELL TRAIT

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The method here presented has made possible a more accurate identification of sickle cells in the blood. It consists of fixing the erythrocytes with formalin after they have been allowed to assume their characteristic form in a test tube sealed with oil. It is also a convenient method for producing large numbers of sickled cells for demonstration purposes and for preparing permanent stained mounts.

The sickling phenomenon develops on standing as in the ordinary sealed slide preparations. The sealing technic, however, is kept constant by keeping the thickness of the oil layer the same every time. Sealing blood samples with paraffin oil in tubes for the exclusion of oxygen and air is very common and can be easily adapted for the production and demonstration of sickling.

Physiologic saline-citrate solution was used as an anticoagulant for the blood and medium for the cells. The present data indicate that sickling is more dependent upon reduced partial pressure of gases, particularly oxygen, than upon the type of medium in which the cells may be suspended. For an account of the conditions favoring and disfavoring sickling, the reader is referred to the reports of Huck,[5] Hahn and Gillespie,[4] Hahn,[3] and Pollock and Dameshek.[6]

The property of formaldehyde to preserve the deformity of sickling was probably first observed by Hahn and Gillespie[4] and later used for this purpose by Hahn in his gas method of producing sickle cells. It has since been recognized by pathologists in handling post mortem material. After adding sodium chloride (8.5 grams per liter) to ordinary 10 per cent neutral

formalin to prevent hemolysis, the results obtained by it were so good that it was adopted without further change.

DETAILS OF THE TEST

Apparatus and reagents

(1) Small test tube, 4 x 1 cms.

(2) Physiologic saline citrate. This may be prepared by mixing equal quantities of normal saline and 3 per cent sodium citrate.

(3) Paraffin oil.

(4) Saline-formalin fixative. Add 0.85 grams of sodium chloride to 100 cc. of 10 per cent neutral formalin.

(5) Glass slides, coverglasses, lancet to prick finger, three small bottles and three small drawn glass pipettes equipped with rubber nipples, and a microscope.

The saline-citrate, the paraffin oil, and the formalin are to be kept in separate bottles, stoppered and labelled. One pipette is to be used for handling the saline citrate solution, one for the paraffin oil, and one for the formalin. Mark these pipettes appropriately because a trace of formalin in the blood prior to sickling may prevent the deformity. Before starting the test, place from 0.2 to 0.5 cc. of saline citrate in the tube to receive the fresh blood.

Procedure

Clean and prick the finger as in collecting blood for a count. Wipe the finger dry and collect one or two drops of blood in the test tube containing the saline citrate. Invert to mix. Cover with sufficient oil to make a layer 1 cm. thick. Make sure no bubbles of air are under the oil. Let the preparation stand at room temperature for twenty-four hours, then introduce 0.2 to 0.5 cc. of the formalin solution beneath the oil layer by means of the formalin pipette. Thoroughly mix by forcing the liquids in and out of the pipette several times. Do not break up the oil layer for fear of letting air in too soon. Two or three minutes or more should be allowed for fixation. After this period the suspension is mixed again with the formalin pipette to insure a uniform distribution of cells. Remove a few drops from the tube, wipe away the excess oil from the tip, and place a drop on a glass slide. Cover and examine. The percentage is calculated in the manner of the differential leukocyte count.

If it is desired to measure the blood and the solutions accurately, it may be done with a hemoglobin pipette for the blood and 1 cc. pipettes, graduated into tenths, for the solutions. It will be found that 20 cmm. of blood in the solutions described above make a very satisfactory cell suspension for microscopic observation.

Permanent preparations are made from the suspension on coverglasses like an ordinary fresh blood film. The smears are dried in air and fixed by flame.

Blood cells treated with formalin are not well tinted in Wright's stain. Excellent stains may be made by using the hematoxylineosin technic, but if it is desired to stain only the erythrocytes, a simpler method consists of staining with basic fuchsin or some similar dye. To use fuchsin, flood the smear with a 1 per cent aqueous solution for 15 to 30 seconds. Pour off, wash in water, and differentiate by flooding with 95 per cent alcohol for 30 to 60 seconds. Destaining in alcohol is to be controlled microscopically before mounting. If the cells are too pale, restain and differentiate less. When the staining is satisfactory, wash in water, blot, dry, and mount in balsam.

During the course of the investigation it happened that none of the subjects, selected in a routine manner, had a history, physical signs, or blood picture suggestive of sickle cell anemia. They were all hospital patients; a large number were maternity cases, a number were men and women in the medical and surgical wards, and the rest were children, including several new born.

The control tests were made by the ordinary sealed moist preparations. At the same time that a blood sample was collected for the tube method, a fresh drop from the same finger puncture was placed upon a coverglass. The coverglass was quickly inverted upon a clean slide. When the spreading was complete, the edges of the preparation were thickly sealed with liquid asphaltum. A few minutes later the edges were inspected for any pores or crevices and the spread was examined for poikilocytosis, aniscocytosis, and crenation. Nothing was found to confuse the examination later for sickling. After waiting twenty-four hours the spreads were re-examined for sickling and for the effects of leakage. The sealing was considered tight in every case.

The adequate sealing of each smear preparation was considered important. Asphaltum was selected because it was believed to be a better sealing substance for smear preparations than vaseline or paraffin.

OBSERVATIONS

Thirteen individuals with sickle cell trait were found in the group of 100 negroes examined by the sealed tube method; only nine were found by the sealed smear method. Twelve of this group were in the third decade of life and under; one a man 64

years old. The incidence of sickle cell trait in the group as a whole was 13 per cent; in children under the age of twelve, 14 per cent; in males, 13.3 per cent; in females, 13 per cent. The incidence in thirty-five maternity cases was 20 per cent. The number examined, however, was small and the incidence should be verified in a larger series. One new born, in the five examined, had the trait.

Differential Cell Findings

Classification of the erythrocytes: In performing the differential count it was necessary to classify every cell that was observed. Crescentic, star-shaped, holly leaf-shaped, and oat-shaped cells were placed in a group together as typical sickle cells. All other erythrocytes having peculiar shapes, but not having pointed processes, were grouped as indeterminated cells because they could be interpreted either as partially sickled forms or atypically crenated cells. The forms encountered in this group were numerous. There were forms that strikingly resembled the characteristic sickle cell but the change apparently stopped too short for this interpretation. There were other forms that resembled the fragmenting and tailing poikilocytes seen in certain phases of pernicious anemia. Finally there were forms that suggested atypical crenation but very seldomly a typically crenated cell was seen. Crenated cells were found only in the sealed smear preparations. Whatever may be the conditions of the test, the presence of indeterminate cells in the preparation is not precisely accounted for one way or the other as the shapes here described developed in twenty-four hours upon standing at room temperature sealed from the atmosphere.

Sickle cells: In the nine sealed smear preparations (see table 1) that contained sickle cells no two of them had findings that were similar. The percentage of sickle cells in the series varied from 3 per cent to 85 per cent with an average of 26 per cent for nine cases.

The findings in the tube preparations were more uniform. There were five instances of 98 per cent sickling, and in eleven of the thirteen cases the number of sickle cells varies between 85

per cent and 99 per cent. The total number was more than four times that found in the same group by the slide method. The average for the thirteen cases was 77 per cent.

Indeterminate cells: In the slide preparations indeterminate cells were more frequently found than sickled cells, and commonly in greater numbers. In those preparations that contained no or few typically sickled cells, the number of indeterminate forms

TABLE 1

EVIDENCE OF SICKLE CELL TRAIT IN 100 NEGROES

Males, 30 (positive, 4); Females, 70 (positive, 9), Maternity cases, 35 (positive, 7); Children, 21 (positive, 3)

AGE—SEX	CLINICAL DIAGNOSIS	DIFFERENTIAL CELL FINDINGS					
		CONTROLS*			TEST TUBE		
		Sickle cells	Indeterminate cells	Normal cells	Sickle cells	Indeterminate cells	Normal cells
		per cent	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*
26 F	Pregnancy	0	94	6	98	0	2
9 days M	Normal	5	2	93	13	0	87
20 F	Pregnancy	15	80	5	98	0	2
20 F	Pregnancy	0	95	5	95	0	5
64 M	Prostatic hypertrophy	50	30	20	94	0	6
14 F	Pregnancy	5	0	95	99	0	1
29 M	Lung pathology ?	3	0	97	3	0	97
29 F	Pregnancy	25	64	11	85	12	3
20 F	Pregnancy	16	60	24	95	0	5
21 F	Pregnancy	0	22	78	28	72	0
32 F	Neurological ?	0	0	100	98	0	2
5 F	Bronchitis	85	10	5	98	0	2
3 F	Otitis media	28	30	42	98	0	2
Averages		18	37	45	77	7	16

* Sealed moist preparation made simultaneously with the tube preparation.

was very high. They were found in ten smear preparations and in only two tube preparations. In several instances (see table 1) the number of indeterminate forms in the smears is sufficiently high to be comparable to the number of typically sickled cells in the corresponding tube preparations. The total number obtained by the slide method is more than five times as great as that found by the tube method.

The apparently normal erythrocytes are placed in a third group. In nearly every slide preparation the number of these cells is greater than that in the corresponding tube preparation of the same blood. The total number of apparently normal cells obtained by the slide method is more than twice that found by the tube method.

DISCUSSION

The finding of 26 per cent sickled cells, in the slide preparations of the individuals with sickle cell trait, is in agreement with the 25 per cent obtained by the same method in similar subjects by Huck and Diggs.[2] The 77 per cent, however, in the same group by the tube method is much higher. It compares better with the 75 per cent obtained by these observers for those patients having moderate symptoms of sickle cell anemia. This evidence supports the opinion of Cooley and Lee,[1] Stewart,[7] and Hahn, that there is no definite relationship between the severity of the condition and the number of erythrocytes which assume the sickle cell appearance in vitro. This finding also may be taken as proof that the low findings in the sealed smear preparations are due largely to inadequacy of the method.

The greater capacity of the tube method for the production of typically sickled cells is easily seen by a comparison of the results of the two methods. By the tube method the number of sickled cells is much higher and the number of indeterminate forms is much lower. As judged by the production of typically sickled cells, the evidence of sickle cell trait is more frequently demonstrated by the tube method. No explanation is offered for these differences in the two methods other than the more accurate sealing in the tube method. Why this should be, is easily explainable by using only the two major factors concerned in the test. The hypothesis that the cells themselves metabolically reduce the oxygen pressure in the sealed moist slide preparations is applicable to the tube method. The test therefore depends upon a progressive oxygen consumption by the cells and an exclusion of oxygen from the cells by a sealing technic. The reduction of oxygen pressure thus brought about is a gradual one, and the shapes that the cells ultimately assume are brought

about by a gradual change from the circular form. It is very likely that the indeterminate cells commonly seen in smear preparations represent intermediate sickling changes from the circular form because the oxygen pressure at the time of examination is not sufficiently low to complete the change. Even if there is no perceptible leakage of air through the seals it is quite probable, from the results here presented, that enough oxygen can diffuse through to prevent the sickling phenomenon from going to completion.

If the indeterminate cells, which may be the only type present in a sealed preparation, should prove to be partially sickled forms it will have an important bearing upon the incidence. Diggs obtained an incidence of 8.2 per cent in 827 negroes by taking every precaution against air leakage through the seals of vaseline and paraffin. This figure is appreciably higher than the 6 or 7 per cent generally reported, but is comparable to the 9 per cent in the present series of 100 negroes by the slide method where asphaltum was used for the sealing substance. The 13 per cent by the tube method in the same group is very likely the result of the more accurate sealing with paraffin oil.

CONCLUSIONS

1. A test tube method for the production and demonstration of sickle cells is described. Every phase of the test is easily controlled and standardized.

2. The results of 100 tests by this method are compared with the results of the sealed smear method in the same group at the same time.

3. An incidence of 13 per cent is reported for the sickle cell trait in 100 negroes.

4. When the sickle cell trait exists, 77 per cent or more of the erythrocytes may show sickling by the tube method. By the slide method the trait may not be demonstrated at all in many cases.

REFERENCES

(1) Cooley, T. B., and Lee, Pearl: The sickle cell phenomenon. Am. Jour. Dis. Child., **32**: 334–340. 1926.

(2) DIGGS, L. W.: The sickle cell phenomenon. I. The rate of sickling in moist preparations. Jour. Lab. and Clin. Med., **17:** 913–920. 1932.

(3) HAHN, E. V.: Sickle-cell (drepanocytic) anemia, with report of a second case successfully treated by splenectomy and further observations on the mechanism of sickle-cell formation. Am. Jour. Med. Sc., **175:** 206–217. 1928.

(4) HAHN, E. V. AND GILLESPIE, E. B.: Sickle cell anemia, report of a case greatly improved by splenectomy. Experimental study of sickle-cell formation. Arch. Int. Med., **39:** 233–254. 1927.

(5) HUCK, J. G.: Sickle cell anemia. Bull. Johns Hopkins Hosp., **34:** 335–344. 1923.

(6) POLLOCK, L. H., AND DAMESHEK, W.: Elongation of the red blood cells in a Jewish family. Am. Jour. Med. Sc., **188:** 822–834. 1934.

(7) STEWART, W. B.: Sickle cell anemia, report of a case with splenectomy. Am. Jour. Dis. Child., **34:** 72–80. 1927.

MALIGNANT HEMANGIOMA*

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For the most part, hemangiomas show no definite uniform histologic structure, but are simple benign blood vessel tumors with very little stroma. Some of them show masses of new growing capillary blood vessels which expand when they become filled with blood, forming large spaces and are called cavernous hemangiomas. Frequently a more complicated type is found in which a more cellular stroma is seen, but even here the blood vessels become very abundant and overshadow the stroma. Not infrequently multiple hemangiomas of the skin are found, which are explained as congenital formations with their origin in the vascular system in early embryonic life. In the embryo connections occur between the blood and lymphatic vessels and between the arteries and veins which in later development usually become obliterated. Occasionally an opening presists after birth with the formation of an aneurysmal varix or a hemangioma. Even when such occurrence occasionally takes place later in life it is explained on the same basis.

In the many references to hemangiomas there is very little concerning malignant hemangiomas. Jenkins and Delaney[5] in reporting 256 cases of hemangioma without one death say "The prognosis for life is excellent as there were no deaths reported from the disease or the surgical treatment." Pusch[10] reported a uterine neoplasm with an unusual ramified distribution which he called a ramifying angioma and regarded it as benign. Ballinger, Elder and McDonald[2] reported several cases of hemangioma of the bladder with no discussion of malignancy. McLaughlin and Beck[9] successfully treated a multilocular lymphangioma of the

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spleen by splenectomy. Alpers and Pancoast[1] similarly reported a successful operation with complete recovery in a patient with a hemangioma of the vertebra. Ewing[3] referred to a complicated type of hemangioma in which the stroma was quite cellular and blood vessels very abundant and Shennan[11] recorded a marked hyperplasia and proliferation of the blood vessel endothelial cells but neither one reported frank malignancies.

Many years ago Langhans[7] referred to malignancy in hemangioma, describing types of blood tumors which he called vascular tumors with a sacromatous stroma. Others have described similar tumors since.

Livingston and Klemperer[8] reported that hemangioma with metastases had been observed and Karsner,[6] of this type of tumor stated, "it may metastasize without striking alterations in its histology."

Jaffé[4] referred to a blood tumor which was potentially malignant, behaving like a malignant tumor but microscopically did not present the picture of malignancy. Its malignant behaviour was borne out by its recurrence after surgical removal, its local invasive and destructive tendency and its metastases to distant organs. He reviewed the literature quite extensively and reported a case showing multiple hemangiomas of the skin and internal organs in which the point stressed was the multiplicity of a benign tumor rather than distant metastases from a primary focus. While he stated, "at least as far as the hemangiomas with a mature stroma are concerned, their possible formation of metastases is doubtful," he agreed that metastasizing hemangiomas are found, though rarely, and he verified the diagnosis in the case herein reported.

The following case is reported because of the interest in the possibility of metastases in hemangiomas; in this case it is probable that an original blood tumor which presented a malignant picture metastasized to distant organs.

CASE REPORT

A male, aged 64, gave a history of a fall in September 1932, striking the right side of the chest on a golf club which resulted in some pain, not of great severity.

In April 1933 he again struck the same side of the chest by a fall on an auto bumper. The pain was only slightly increased and about two weeks later, May 9th, he first noticed a lump over the ribs in the right chest at the site of the previous injuries. At this time he consulted his physician who explained the lump as a callous formation of a fractured rib. On May 23rd he consulted another physician* who felt and opened a fluctuating mass over the ninth rib anteriorally, from which necrotic bone tissue was curretted. At the same time the patient complained of a painful contracture of the left leg. About July first a mass was palpable in the left iliac region which was rather firm and grew quite rapidly attaining the size of a grape-fruit within a very short time. At that time an examination of the blood revealed: erythrocytes, 2,500,000; leukocytes, 14,000; hemoglobin, 45 per cent (Sahli). The patient also complained of a sense of fullness in the left side of the abdomen, and indeed a very large spleen was definitely palpable. Cystocopic examination revealed no change in ureters and kidneys. He lost weight very rapidly, and continued a rapid down hill course. A differential count performed three days before death showed: polymorphonuclears, 61 per cent; lymphocytes, 32 per cent; monocytes, 6 per cent; eosinophiles, 1 per cent; no immature cells noted. He died August 10, 1933.

NECROPSY REPORT

On post mortem examination, the essential finding was the demonstration of an apparent malignant blood tumor. Over the fifth and sixth ribs on the right chest, there was an open 1.5 cmm. rounded erosion with raised edges, from which a thick bloody fluid exuded. This ulcerated area extended through the chest wall involving the parietal pleura at which point there was an elevated rounded fluctuant growth measuring 3 cmm. in diameter. On cut section this growth was filled with dark fluid blood and a very friable, spongy, reddish brown necrotic-like substance. A similar, but smaller growth of the pleura, was found at the level of the third rib on the same side, and another at the level of the fifth rib on the left side. The spleen was involved in a large irregular soft, purple gray mass weighing 560 grams, and only one pole at one end was recognizable as spleen.

On cut section the splenic pulp was replaced by soft, spongy material similar to that found in the pleural tumor, and large quantities of dark fluid blood escaped. Another mass, about the same size as the splenic one, was found over and completely eroding through the left iliac bone; cut section revealed large sponge-like spaces filled with dark fluid blood. The liver weighed 1,500 grams, and the capsule was everywhere studded with small rounded, reddish blue discolorations up to 9 mm. in diameter.

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* I am greatly indebted to Dr. Homer O. Dolley of Bloomington, Illinois, for his coöperation in submitting the history of, and with whose permission, this case is reported.

It was soft and boggy and the cut surface was diffusely covered with uniform sponge-like openings all filled with dark fluid blood.

Microscopically these tumors all presented the same picture: large masses of undifferentiated tumor cells which were seen tending to blood vessel formation, and large blood spaces filled with blood. No definite anaplasia was seen in the individual cells but the picture in general was one which presented a definite invasive and destructive tendency.

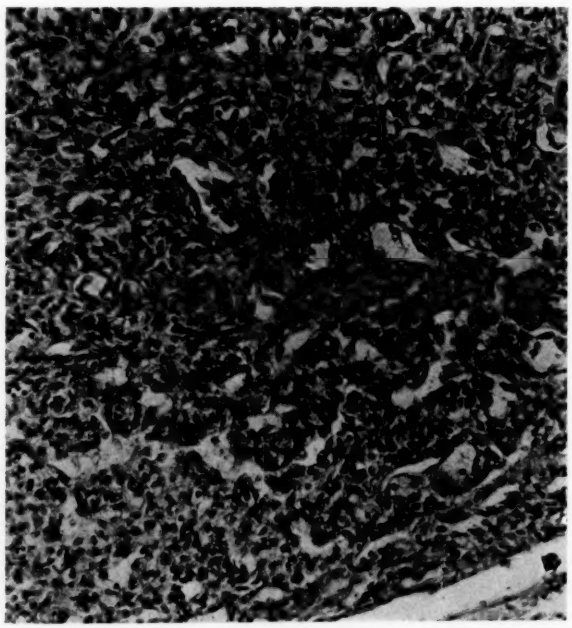

FIG. 1. TUMOR OF PLEURA
Indifferent rapidly growing cells with no blood vessel formation

In figure 1 of what may be considered the original tumor, that of the pleura, the tumor cells are of indifferent, rapidly growing type and little blood vessel formation is seen. But as shown in the section of the liver (fig. 2) these cells may be seen in the formation of blood vessels and resulting large blood spaces. The tumor process was evidently a similar one in both sections; the undifferentiated tumor cells represented the earlier stage and the blood vessels and blood spaces represented the later stage.

Because of the lack of anaplasia it may be argued that this tumor is pathologically non-malignant, but the invasive tend-

ency of these cells, with the rapidly growing tumor mass of the spleen and iliac bone, both of which may reasonably be regarded as metastases, justify the contention that this tumor pursued a malignant course.

Some question may be raised as to the actual metastases in this case because of the assumption that malignant cells from a blood

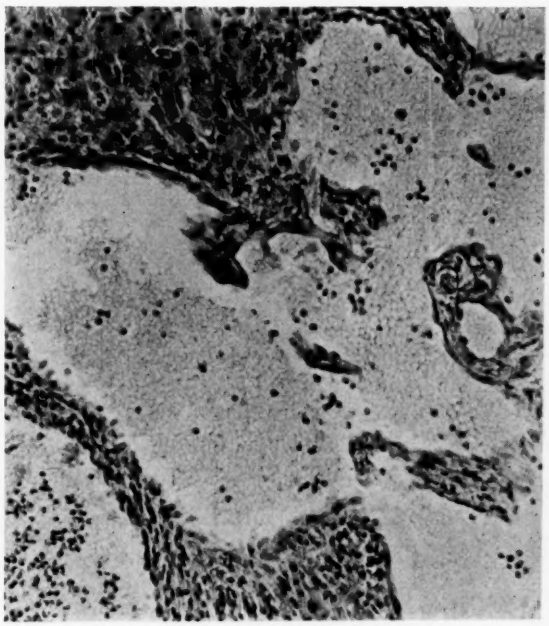

FIG. 2. TUMOR OF LIVER

Indifferent rapidly growing cells with blood vessel and space formation

vessel tumor were transplanted from a primary focus to distant organs by way of the lymph or blood stream and such implantation, according to literature, does not occur. In fact no definite record was found of such demonstration. The marked difference however in size of the tumors together with the expansive and invasive growth indicate that these tumors were not independent formations.

SUMMARY

A case of fatal hemangiomas of the pleura, spleen, liver and iliac bone is described. Microscopically the cells of these tumors showed no definite anaplasia but did present evidence of an invasive and destructive growth. These observations indicate that these tumors were not simultaneous and independent formations, as found in multiple-hemangiomas, but rather a single focus in the pleura with metastases to other organs.

REFERENCES

(1) Alpers, B. J. and Pancoast, H. K.: Haemangioma of the vertebrae. Surg. Gyn. and Obst., **55:** 374–376. 1932.

(2) Ballenger, E. G., Elder, O. F., and McDonald, H. P.: A case of cavernous hemangioma of the bladder. Am. Jour. Surg., **17:** 409–412. 1932.

(3) Ewing, James: Neoplastic diseases. 2nd Ed. Philadelphia: W. B. Saunders Co., 1922, pp. 1054.

(4) Jaffé, R. H.: Multiple hemangiomas of the skin and of the internal organs. Arch. Path., **7:** 44–54. 1929.

(5) Jenkins, H. P., and Delaney, P. A.: Benign angiomatous tumors of skeletal muscles. Surg. Gyn. and Obst., **55:** 464–480. 1932.

(6) Karsner, H. T.: Human pathology. Philadelphia: J. B. Lippincott Co., p. 364, 1926.

(7) Langhans, Theodor: Casuistische Beiträge zur Lehre von den Gefässgeschwülsten. Virchow's Arch. Path. Anat., **75:** 273–300. 1879.

(8) Livingston, S. F., and Klemperer, Paul: Malignant angiomas, with reference to the question of sarcoma due to roentgen ray. Arch. Path. and Lab. Med., **1:** 899–910. 1926.

(9) McLaughlin, C. W., and Beck, J. S. P.: Multilocular cystic lymphangioma of the spleen. Arch. Path., **15:** 655–664. 1933.

(10) Pusch, L. C.: Report of a case of ramifying angiomyoma of the uterus. Am. Jour. Obst. and Gyn., **24:** 907–910. 1932.

(11) Shennan, Theodore: Histologically non-malignant angioma with numerous metastases. Jour. Path. and Bact., **19:** 139–154. 1914.

EDITORIAL

The Evaluation of Serodiagnostic Tests for Syphilis in the United States

When Dr. Walter M. Simpson, as president of the American Society of Clinical Pathologists in 1932, began plans for a serologic conference, to be conducted by our society, he little dreamed of the ramifications to which the proposal would lead. It was not feasible to hold the conference at the Milwaukee meeting in 1933, as it was at first hoped. A committee of the Society, consisting of Dr. Walter M. Simpson, and Dr. Arthur H. Sanford carried the matter to Surgeon-General Hugh S. Cumming, of the United States Public Health Service. Through his whole-hearted support, the expenses of the plan were met by the Public Health Service. The Surgeon-General appointed a committee consisting of H. H. Hazen, A. H. Sanford, F. E. Senear, W. M. Simpson, and detailed R. A. Vonderlehr of the Public Health Service as executive officer for the project. The details of the entire work were practically all evolved by Dr. Vonderlehr, and the study was made in the early months of 1935. As the scheme for collecting blood and spinal fluid, and sending it simultaneously to 13 different serologists unfolded itself, the committee became increasingly more enthusiastic about the value of the undertaking. It was no small task to furnish satisfactory samples of blood and spinal fluid from more than 1200 carefully selected donors to the participating serologists. The committee was particularly impressed with the fine spirit of coöperation shown by all of the serologists, and clinicians that were concerned with this study. The final evaluation of the results proved a most interesting, though arduous task. The committee met in Washington, April 15 to 18, with Dr. G. W. McCoy, Director of the National Institute of Public Health, acting as chairman for the Surgeon-General of the Public Health Service.

The results of testing 14,252 comparable blood samples, and 2,860 comparable spinal fluid samples were examined critically. Key letters had been assigned to each laboratory by the executive officer and the name of the participating serologist was not revealed to the committee until the study was completed. The result of this evaluation procedure has been reported to the American Society of Clinical Pathologists at the round table meeting in Atlantic City, June 7, 1935, and a scientific exhibit presented at the meeting of the American Medical Association.

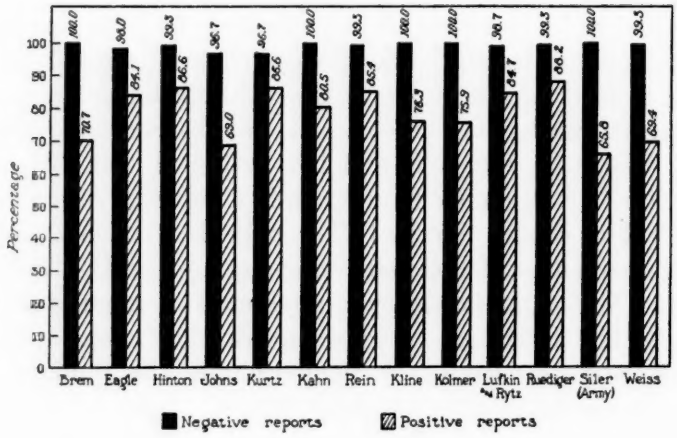

FIG. 1. SENSITIVITY OF BLOOD TESTS BASED ON ABILITY TO DETECT SYPHILIS CONTRASTED WITH THE SPECIFICITY OF BLOOD TESTS BASED ON ABILITY TO EXCLUDE SYPHILIS

The preliminary report has appeared in Venereal Disease Information published by the Public Health Service, and the Journal of the American Medical Association, June 8, 1935. The complete report will be published in a special Public Health Service bulletin. A summary of the results of specificity and sensitivity is shown in figure 1.

It is evident that all of the serologic methods that have been developed in the United States show a satisfactory specificity in the high percentage of negative results in normal non-syphilitic individuals. The percentage of sensitivity is also very con-

vincing, although here more variation is evident. Flocculation methods show a high percentage in this respect, though mention should be made of the ingenious complement fixation method of Ruediger with high degrees of specificity and sensitivity. In contrast to this the Army method is not so sensitive, but yielded no false positive results with blood from normal non-syphilitic donors, the sort of test that is desired for a soldiers' service record.

No satisfactory evaluation could be made of the nonspecific reactions in various diseases other than syphilis, as the committee felt that sufficient data were not collected, with the exception of the cases of leprosy. Though this last named group is not large, it is evident from this study that leprosy uncomplicated by syphilis will produce a high percentage of positive reactions with all methods.

Many problems have presented themselves in connection with this the first evaluation of serodiagnostic tests for syphilis in the United States, and the Society will be interested to know that Surgeon-General Cumming has considered favorably the continuance of a committee for carrying on further investigations.

A. H. SANFORD.

BOOK REVIEWS

The Brain as an Organ; Its Postmortem Study and Interpretation. By Frederick and Florence Wertham. New York: MacMillan Co., pp. xviii + 538, plates 166, 1934. $7.50.

The object of this volume is an excellent one. The authors compare the reactions of the brain to those of other organs of the chest or abdomen. This object, had it been carried sufficiently far, would have simplified the gross and microscopic study of the brain and brought the study of the central nervous system within the field of the general pathologist. They show that the brain like other organs reacts in a limited way to inflammation, degeneration, and injury. Much confusion has arisen in neuropathology due to neuropathologists giving varying descriptions and names to the same lesion when seen at different stages of its evolution. The authors of this book have gone a long way in endeavouring to clear up some of this confusion, and for this alone it should be read, and also because of the stimulus it offers. The volume embodies this original idea, but it goes much further; as a review of our present knowledge of neuropathology and histology it is to be recommended. There is in addition a good review of the literature, particularly European literature, included in the text. The illustrations at the end of the book are well done and should be helpful in interpreting what is seen under the microscope.

J. W. Kernohan.

A Textbook of Biochemistry. Edited by Benjamin Harrow and Carl P. Sherwin. Philadelphia and London: W. B. Saunders Co., 1935, pp. 797. $6.00.

This book was prepared to meet the requirements of modern courses in biochemistry and if one accepts it as a suitable text for medical students, the conclusion is inevitable that they have ad-

vanced greatly during the last few years. One has only to peruse the chapter dealing with some aspects of the physical chemistry of amino acids and proteins, or the one on the nucleic acids, to be convinced of the validity of this statement. The book is an advanced treatment of the subject of biochemistry and is suitable for very advanced students, investigators and some teachers. Inclusion of chapters on the cell, biochemistry of bacteria, yeasts and molds, detoxication, immuno-chemistry, chemistry of the integument and brain indicate something of the nature of the material presented. There are numerous references to modern literature and each chapter takes the form of a miniature monograph with, as is usually the case in compiled volumes, little to connect it to other chapters. The book will have its chief value as a reference work; however, serious students will continue, as in the past, to go to the original source.

The Kidney in Health and Disease. Edited by Hilding Bergland and Grace Medes in collaboration with many authors. Philadelphia: Lea & Febiger, pp. vi–754. 1925. $10.00.

This volume is the outgrowth of a symposium on the structure and function of the kidney in health and disease which was held in Minneapolis in 1930. Shortly before publication, each chapter was revised and several contributors have been added since the symposium was held. There are forty-five chapters written by forty-one scientists. Part I deals with the anatomy and physiology of the kidney; part II with clinical aspects of renal function; part III with Bright's disease and various other pathologic renal conditions; part IV with albuminuria and edema; part V with ocular changes in Bright's disease, and part VI with clinical aspects of Bright's disease.

The book is liberally illustrated; there are many charts and tables. Each chapter is annotated with bibliographic references and altogether the volume makes a valuable contribution to the understanding of the function and pathology of the kidney. Most of the chapters contain original material not published elsewhere and in that sense they are more or less complete monographs dealing with a particular phase of the subject. The

book should find a place on the shelves of every physiologist, pathologist, and practitioner of medicine.

The Harvey Lectures. By Various Authors. Baltimore: The Williams & Wilkins Co., pp. 262. 1935. $4.00.

This volume is dedicated to Alfred Fabian Hess and contains a brief biography of him.

The first lecture is by R. E. Dyer in which he discusses the characteristics of Rocky Mountain spotted fever, of epidemic and endemic typhus fever, and the epidemiology and symptoms of the diseases. The second contribution, by W. M. Clark, is on the potential energies of oxidation-reduction systems and their biochemical significance and is an involved treatment of the physicochemical nature of this reaction. The lecture by R. G. Harrison deals with heteroplastic grafting in embryos, chiefly of the limb buds, gills, skin, and sensory organs in the urodeles. The essay on estrogenic substances, by E. A. Doisy, in its major part deals with theelin and its chemical structures. The lecture by E. A. Graham, on the clinical application of some recent knowledge of the biliary tract, primarily concerns itself with study of excretion of cholesterol by the gallbladder and the deposit of this substance in the mucosa (cholesterosis) as influenced by inflammation and stasis. Graham supports Sudler's contention of the lymphatic anastomosis between the gallbladder and the liver.

G. L. Streeter, writing on the significance of morbid processes in the fetus, suggests that morbid changes in the fetus are attributable to inherent abnormalities and deficiencies in the germ plasm rather than to extrafetal conditions. Such abnormalities may not be manifested at birth, but show up later in the adult.

The lecture by T. M. Rivers deals with the general theory of filtrable viruses and with his more recent experiments on psittacosis. He points out that viruses have not been cultivated in the absence of living cells.

The last contribution, on the nervous mechanism of cardiovascular control, by D. W. Bronk, is a discussion of the receptor system in the walls of blood vessels which are responsible for the tonic contraction of the vessels and the accelerated influence on

the heart, balanced by the inhibition of the vagus nerve. The author maintains that circulation is under self-initiated control.

The Patient and the Weather, vol. 2, Autonomic Disintegration. By William F. Petersen. Ann Arbor: Edwards Brothers, Inc., pp. xx + 530, 1934. $6.50.

Case reports and discussions, together with numerous tables, figures, and charts in an attempt to correlate health, disease, and symptoms with the weather.

NEWS AND NOTICES

The Fourteenth Annual Convention of the American Society of Clinical Pathologists held at Atlantic City, June 7 to 9, 1935, was preceded by a tissue study period lasting four days in New York City. At this study period there was an attendance of about one hundred and twenty-five. The headquarters were located in the New York University, College of Medicine, and sessions were held in the General Memorial Hospital, Cancer Institute, Bellevue Hospital, Prudential Life Insurance Company, and Lennox Hill Hospital. Included in the study period were many lectures and discussions by outstanding pathologists in New York, examination of slides and methods of obtaining tissue, a symposium on tumors and tumor-like lesions of the lymphoid system, demonstrations of postmortem methods, frozen section methods, and a laboratory demonstration of tumors of the mouth. It is evident that the study period was a successful undertaking and marks the second of those which have been conducted under the auspices of the Society.

At the annual convention in Atlantic City, more than one hundred and sixty-five men registered and the sessions were noteworthy on account of the large attendance at the individual meetings. It is difficult to point to any one session which was outstanding but certainly there should be mentioned the report of the Serologic Conference of which Dr. R. A. Vonderlehr was chairman. The editorial in this issue of the JOURNAL gives some of the details of that conference. A symposium on cholesterol attracted a great deal of attention and the papers presented at that time will be published in a forthcoming issue of the JOURNAL.

The Ward-Burdick medal was awarded to Dr. John A. Kolmer for his work on poliomyelitis vaccine, the gold medal for scientific exhibits to Dr. Russell Haden, the silver medal to Dr. Anna M. Young and her associates, and honorable mention to Dr. E. von Haam.

Dr. Geo. W. McCoy of the Hygienic laboratory was elected to honorary membership and the following were elected to membership:

L. L. Adamkiewicz, San Diego, Calif.
J. A. Beauchemin, Middletown, Conn.
M. P. H. Bowden, New Orleans, La.
W. L. Brosius, Detroit, Mich.
T. H. Byrnes, Durham, N. C.
M. Criscitiello, Pittsfield, Mass.
L. E. Dickelmann, Oshkosh, Wis.
L. Y. Dyrenforth, Jacksonville, Fla.
J. L. Ford, Lancaster, Pa.
I. A. Gaspar, Rochester, N. Y.
R. H. Goodale, Worcester, Mass.
S. E. Gould, Detroit, Mich.
B. M. Hathaway, Akron, Ohio
Lee Howard, Savannah, Ga.
J. A. Kasper, Detroit, Mich.
G. J. Kastlin, Pittsburgh, Pa.
S. D. Katz, St. Louis, Mo.
V. H. Keiller, Houston, Texas
P. J. Kennedy, Lansdowne, Pa.
M. J. Kilbury, Little Rock, Ark.
Robert Koritschoner, Kansas City, Mo.
L. D. Larimore, New York, N. Y.
S. A. Levinson, Chicago, Ill.
I. M. Lickly, Muskegon, Mich.
Aldea Maher, New Orleans, La.
Morris Maslon, Glens Falls, N. Y.
Kendrick McCullough, Burlington, Vermont
Thomas McCurdy, Omaha, Neb.
Maurice Morrison, Brooklyn, N. Y.
T. C. Moss, Memphis, Tenn.
H. S. Nauheim, Tulsa, Okla.
E. E. Osgood, Portland, Ore.
F. P. Parker, Emory University, Ga.
H. M. Ray, Pittsburgh, Pa.
R. S. Rosedale, Buffalo, N. Y.
J. P. Tollman, Omaha, Neb.
W. A. Wall, Cortland, N. Y.
I. M. Wise, Mobile, Ala.
K. Y. Yardumian, Pittsburgh, Pa.

The following officers were elected:

President: Foster M. Johns.

President-Elect: Roy R. Kracke.

Vice-President: R. A. Kilduffe.

Executive Committee (3 years): F. H. Lamb, L. W. Larson.

Board of Censors (3 years): O. W. Lohr, I. A. Nelson.

Board of Registry (3 years): Philip Hillkowitz, Kano Ikeda.

Further details of the meeting with the secretary's report will be published in a later issue of the JOURNAL.